EXHIBIT C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1 CASES**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

NOTICE OF ADOPTION OF PRIOR EXPERT REPORTS AND TESTIMONY OF PEGGY PENCE, Phd, RAC, FRAPS

Comes now, the Plaintiffs, and hereby designate Dr. Peggy Pence's prior expert reports, attached hereto as Exhibit 1[1], as her general expert reports to be used at the discretion of the individual plaintiffs in the cases designated in Wave 1, Wave 2, and any future waves of Ethicon cases designated by the Court.

Dated: February 1, 2016

Respectfully submitted,

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[1] Exhibit 1, Report from *Lewis*, 10/24/2013.

PEGGY PENCE, PhD, RAC, FRAPS
EXPERT WITNESS REPORT

RE: TENSION FREE VAGINAL TAPE (TVT) SYSTEM
PRODUCT LIABILITY LITIGATION
vs. ETHICON, INC.
AND JOHNSON & JOHNSON
(Collectively referred to in this Report as Ethicon)

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List of Key Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
AHWP	Asian Harmonization Working Party
BLA	Biologics License Application
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CRO	Clinical Research Organization
CSUCI	California State University Channel Islands
CSUPERB	California State University Program for Education and Research in Biotechnology
CT	Cytotoxicity
DHCP	Dear Health Care Professional
DDUPSA	Division of Device User Programs and Systems Analysis
DFU	Directions for Use
DIA	Drug Information Association
DIS	Detrusor Instability Score
DSC	Differential Scanning Calorimetry
EWHU	Ethicon Women's Health and Urology
FAERS	FDA Adverse Event Reporting System (formerly AERS)
FDA	U.S. Food and Drug Administration
FDAMA	FDA Modernization Act of 1997
FDCA/FD&C Act	Federal Food, Drug, and Cosmetic Act
FRAPS	Regulatory Affairs Professionals Society Fellow
FTC	Federal Trade Commission
GAO	Government Accountability Office
GBP	British Pound
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HHS	Department of Health and Human Services
ICDs	Implantable Cardioverter Defibrillators
IDE	Investigational Device Exemption
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IIQ-7	Incontinence Impact Questionnaire-Short Form
IL	Interleukin
IMDRF	International Medical Device Regulators Forum
IMT	Inflammatory Myofibroblastic Tumor
Inc.	Incorporated
ISO	International Organization for Standardization
IV	Intravenous
J&J	Johnson & Johnson Company
KOL	Key Opinion Leader
LCM	Laser Cut Mesh
LC	Laser Cut
LLC	Limited Liability Company
MAUDE	Manufacturer and User Facility Device Experience Database

MCM	Mechanical Cut Mesh
MDA	Medical Device Amendments
MDR	Medical Device Reporting
MedDRA	Medical Dictionary for Regulatory Activities
MS	Master of Science
NCA	National Competent Authority
NDA	New Drug Application
NHDS	National Hospital Discharge Survey
NSE	Not Substantially Equivalent
OCRA	Orange County Regulatory Affairs Discussion Group
ODE	Office of Device Evaluation
OTC	Over-the-Counter
PDP	Polyethylene
PET	Polyethylene Terephthalate
PhD	Doctor of Philosophy
PHN	Public Health Notification
PG	Polyglactin
PMA	Premarket Approval Application
POP	Pelvic Organ Prolapse
PP	Polypropylene
PTFE	Polytetrafluorethylene
PVS	Pubovaginal Sling
QOL	Quality of Life
QSR	Quality System Regulation
RAC	Regulatory Affairs Certification
RAPS	Regulatory Affairs Professionals Society
RCT	Randomized, Controlled Clinical Trials
SCC	Squamous Cell Carcinoma
SE	Substantially Equivalent
SEM	Scanning Electron Microscopy
SG2	GHTF Study Group 2
SMDA	Safe Medical Devices Act of 1990
SPARC	Supra Pubic Arc
SUI	Stress Urinary Incontinence
S.W.O.T.	Strengths, Weaknesses, Opportunities, Threats
TGA	Thermogravimetric Analysis
TOT	Transobturator Tape
TVT	Tension-free Vaginal Tape
TVT-O	Tension-free Vaginal Tape Obturator
UC	Ultrasound Cut
UDI	Urogenital Distress Inventory
UI	Urinary Incontinence
US or U.S.	United States of America
U.S.C.	United States Code
UTI	Urinary Tract Infection
VOC	Voice of Customer
WCQ	Worldwide Customer Quality

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I. CREDENTIALS AND METHODOLOGY

A. Credentials: Qualifications and Experience

I have more than 40 years of experience in the research and development of traditional pharmaceuticals, biotechnology-derived therapeutics (biopharmaceuticals), and medical devices, including in vitro diagnostics. I began my career at Eli Lilly and Company in 1970 in basic immunology research and later transitioned to clinical and regulatory affairs. I subsequently held project management and clinical management positions, from 1983 to 1992, at a number of emerging-growth companies, including Serono Laboratories (U.S. start-up), Triton Biosciences (acquired by Berlex Laboratories, Inc.), and Amgen, Inc.

In 1992, I founded a consulting firm that was incorporated in 1995 as Symbion Research International, Inc., a full-service contract research organization (CRO) and consulting firm. I have been President and Chief Executive Officer since that time. In this position, I provide advice, guidance, and product development services to pharmaceutical/biopharmaceutical and medical device companies in the areas of strategic planning, preclinical testing, clinical trials design and conduct, and regulatory matters involving the U.S. Food and Drug Administration (FDA), as further discussed below. In January 2012, I co-founded Illuminostics, LLC, to provide medical imaging services for clinical trials and to aid in the diagnosis and monitoring of disease in medical practice.

Over the course of my career, I have worked with more than 80 companies and over 90 medical devices, pharmaceuticals (drugs), and biopharmaceuticals (biologic therapeutics), including combination products (e.g., device-drug combination products). I have guided and coordinated product development activities from manufacturing process development through marketing plans and have led development programs for a number of novel therapeutics and medical devices. My medical device experience encompasses all Classes of medical devices: Classes I, II and III. I have broad experience spanning multiple therapeutic areas, including women's health, neurology, neuropsychology, oncology, hematology, infectious disease, rheumatology, nephrology, respiratory disorders, metabolic and growth disorders, gastroenterology, burns, wound healing, and ophthalmology. As regards women's health and wound healing and of particular relevance to the subject matter of this Report, I have designed clinical trials for diseases of the female genital system and have been involved in both preclinical and/or clinical testing of novel medical devices and biologics for wound healing applications, including both deep wounds and surgical incisions.

Notably, the product materials I have reviewed for this Report are the same types of materials I have either prepared or reviewed to assure their accuracy, completeness, and regulatory compliance during the course of my professional career. Further, Ethicon's responsibilities about which I have opined are the same types of responsibilities I have executed over the course of my career in medical product development. I have been an integral or leading member of multiple product development teams to determine the testing requirements for medical devices and drugs/biologics and to make decisions concerning whether additional testing and, if so, what types of additional testing were needed based on initial results of product testing. I have advised manufacturers on the adequacy of proposed medical device labeling. I have also contributed substantially to the development and content of product labeling, including for medical devices. For example, I have prepared clinical study reports and summarized key findings, including safety information, for inclusion in labeling. Further, I have written a number of Investigator's Brochures, which have been termed proto-labeling, because the Investigator's Brochure is the premarketing forerunner of the product package insert and provides the same types of information as the package insert, including adverse reactions, contraindications, warnings and precautions, to advise physicians and other healthcare practitioners of information important to their safe and effective use of medical products. I have analyzed safety information available from clinical trials, the scientific and medical literature, and postmarketing experience to provide this information to the U.S. Food and Drug Information (FDA) and to physicians and other healthcare practitioners to enable their safe and effective use of medical devices and drugs/biologics. I have submitted safety alerts to FDA and physicians about new and important product safety information.

Additionally, I have prepared marketing materials detailing product information. In so doing, I assured the accuracy and fair balance of the safety and effectiveness information presented. Similarly, I have advised companies on the appropriateness of information in press releases and other corporate documents to ensure any potentially misleading or improper information was excluded.

The above is a brief overview of my professional experience relevant to this Report. Further details are described below.

I have performed due diligence evaluations of potential new products to advise sponsor companies or research institutes on product development requirements, including preclinical and clinical testing needs and also regulatory pathway and strategy. I have managed internal and extramural preclinical research programs required for support of product development and manufacturing, clinical research, and business development activities. These have included product characterization, process improvement, stability studies, bioassay development, pharmacology, and preclinical efficacy studies. Additionally, I have developed product-specific, preclinical toxicology testing plans and protocols and have overseen the conduct and reporting of these studies for FDA-regulated products. I have taught Good Laboratory Practice (GLP), which is the regulatory standard for conducting nonclinical (preclinical) laboratory studies to support applications submitted to FDA for research or marketing authorizations. In addition, I have conducted GLP audits of toxicology testing facilities.

Evaluation of preclinical safety and efficacy data are central considerations before initiating human use. Accordingly, I have designed clinical investigational plans and clinical protocols in consideration of preclinical study results, including both efficacy and toxicology data. As a key member of many product development teams, I have been instrumental in the assessment of preclinical data to determine whether the available safety information supported the transition from preclinical to clinical use. Similarly, I have evaluated both preclinical and available clinical safety data to determine whether product safety profiles supported application for marketing authorization and also product development for new clinical uses.

I have designed and managed or directed the conduct of numerous clinical studies, from first-in-man studies of novel therapeutics and medical devices to pivotal studies for marketing approval. This has included performing and/or directing the monitoring, data management, analysis, and reporting of the safety and effectiveness/efficacy data from these studies, ensuring that all activities were performed in compliance with applicable regulations, Good Clinical Practice (GCP), the international regulatory and quality standard for the conduct of clinical trials involving human subjects and other relevant FDA Guidances. Of note, I established, staffed, and directed the first Clinical Quality Assurance and Document Control department at Amgen, a leading biotechnology firm. Further, I have directed collaborative clinical programs with foreign affiliates to reduce overall clinical development time and costs, and enhance quality and usability of data globally for marketing applications.

I have organized and directed meetings of clinical study physicians ("investigators") at the outset of multicenter clinical trials both to obtain concurrence on complex clinical study designs and endpoints and also to instruct these physician investigators on clinical trial requirements and their obligations to comply with the clinical study protocol, all applicable regulations, and GCP. I have performed compliance (quality assurance) audits of clinical investigators' conduct of clinical trials and advised and worked with them and their clinical study staff to correct any deficiencies identified. With respect to FDA inspections of clinical studies, I have been the sponsor representative with lead responsibility for "hosting" the FDA inspection of a sponsor company and clinical investigative sites.

I have provided consultation to multiple companies to establish or evaluate their processes and procedures and, in the latter case, to implement changes necessary to achieve compliance with regulatory and industry standards. In this role, I have developed standard operating procedures and set up operations to perform all aspects of clinical studies and regulatory affairs, including the following activities, among others: clinical protocol design; writing patient informed consent forms (including all known or potential risk information); writing investigator's brochures or report of prior investigations (the forerunner of the package insert/professional labeling); clinical study monitoring and management; data tracking and management; recordkeeping; and reporting of adverse events, Such procedures at Symbion have undergone quality assurance audits by multiple sponsor companies successfully. Further, I have consulted with a multinational pharmaceutical company both to develop implementation strategy and also to implement a global clinical data management system.

I have managed coding of adverse events (using dictionaries designated for regulatory activities) for worldwide clinical programs for the purpose of safety evaluations and regulatory reporting and have collected, investigated, evaluated, and reported safety data to

fulfill both premarketing and postmarketing regulatory obligations. I have advised physician investigators of updated safety information: (i) in the context of providing updated investigator's brochures (which contain similar contents as eventual, professional product labeling [to the extent of known information], in order to provide for safe and effective use of the investigational product); and (ii) through required serious adverse event reports to advise physicians (as well as FDA) of new, critical safety information concerning serious risks with use of the investigational product. In the postmarketing setting, I also have directed the updating of postmarketing surveillance procedures and audited postmarketing adverse reaction records for regulatory compliance. Additionally, I have evaluated post-marketing utilization data.

I have reviewed or contributed substantially to the development of product labeling, including not only adverse reaction content but also contraindications and warnings, nonclinical toxicology and clinical studies information, and product use instructions. I have prepared product launch "backgrounders" for marketing programs and critically reviewed press releases of sponsor companies and other corporate documents prior to their release to ensure any potentially misleading or improper information is excluded.

I have served as the U.S. Agent or authorized representative for FDA matters for both medical device and drug companies, with responsibility for FDA communications and, in the case of medical device companies, for establishment registration and device listing. I have prepared and made numerous regulatory submissions of multiple types to FDA, including premarketing and postmarketing submissions, both for medical devices and drugs/biologics. Additionally, I have advised sponsor companies regarding a broad scope of regulatory requirements, including adverse event reporting, the content of adverse reactions in labels and corrective and preventive actions to address FDA inspectional findings. I have represented sponsor companies during many face-to-face meetings and teleconferences with FDA.

I have served on the Board of Directors or Advisory Board for multiple organizations, including the Biotechnology and Health Programs Advisory Board, California State University Channel Islands (CSUCI); the Clinical Trials Certificate Program Advisory Board, California State University Program for Education and Research in Biotechnology (CSUPERB); and CompassioNow (formerly CareNow Foundation, the purpose of which is to provide medical care to the world's least served). At CSUCI, I also have served as an Advisor for the Master of Science in Biotechnology (MS Biotech) team projects, a curriculum requirement in an academic or industrial location. I have developed and am the instructor for a graduate level course titled "Clinical Trials and Quality Assurance" in the CSUCI MS Biotech program curriculum. As part of this course, I instruct my students on ethics in medical product development and the importance of obtaining and evaluating adequate preclinical safety data before transitioning to human use and assign them case studies relevant to this topic for critical evaluation and class presentation. Additionally, I have developed and am the instructor for a course titled "Clinical Trials Project Management: Managing Clinical Trials" for graduate level students enrolled in either the Program for Applied Biotechnology Studies or the Certificate in Clinical Trials Project Management Program at California State University, Fullerton. I also have served as guest lecturer for the MS Biotech program, CSUCI.

I have often been an invited speaker at industry conferences or workshops on topics current to the development of medical devices, drugs and biologics and have often provided instruction on Good Clinical Practice and other medical product development topics: at sponsor-company, in-house training programs; workshops and seminars; as a guest lecturer and instructor in university graduate or professional programs (as discussed above). I founded the Drug Information Association (DIA) Sub-group and Advisory Committee on Biotechnology and chaired DIA workshops on biotechnology in 1991 and thereafter from 1993 annually through 2001. I have served on the Regulatory Training Course Faculty for the Drug Information Association. I have been an instructor on the medical device premarketing regulations (2008-2009) and postmarketing regulations (2009) for the Orange County Regulatory Affairs Discussion Group (OCRA) course for regulatory professionals preparing to take the U.S. Regulatory Affairs Certification (RAC) examination.

I am RAC-certified, which means I hold the U.S. Regulatory Affairs Certification (RAC, certifying knowledge of U.S. regulations). The RAC credential is the only certification specifically for regulatory professionals in the healthcare product sector. It is conferred by the Regulatory Affairs Professional Society (RAPS) upon successful performance on a standardized proficiency exam, and in consideration of the applicant's education, training, and overall experience. Continuing education and assumption of leadership roles in the profession are necessary to maintain recertification, which is granted every three years, upon submission of appropriate justification. In addition to maintaining the RAC credential, in 2009 I was named a RAPS Fellow (FRAPS), a peer-reviewed credential that recognizes senior regulatory professionals based on experience, contributions, and leadership in the regulatory profession.

In sum, I have the peer-reviewed qualifications of a RAPS Fellow based on professional experience, credentials, and training. Being RAPS certified[1] and a RAPS Fellow,[2] I have achieved the highest level experience within my profession, Level IV, as outlined in the Regulatory Affairs Professional Development Framework.[3]

I earned a Bachelor of Science degree, *magna cum laude*, in Microbiology from Louisiana Polytechnic University and a Doctor of Philosophy (PhD) degree in Toxicology, with a Pharmacology minor, from Indiana University (Medical School campus). I performed my doctoral research predominantly at the Eli Lilly Laboratory for Clinical Research in Indianapolis, Indiana. My doctoral research included the planning and hands-on conduct of all aspects of three clinical pharmacology and toxicology studies. As the prior valedictorian for my high school, I

[1]I tested for and achieved RAPS's Regulatory Affairs Certification ("RAC"). The development of the RAC examination and selection process was based upon extensive research on the scope of practice and specific activities of the profession. This research has been replicated and updated several times, with studies extended to professionals involved with the European, US, and Canadian regulatory systems.

[2]The program recognizes professionals with over 15 years of regulatory experience for their significant contributions and leadership. Fellows receive a prestigious status and serve as important resources for strategic dialogue, mentoring, implementation of special initiatives, and international development. RAPS Fellows, *available at* http://www.raps.org/membership-amp-benefits/raps-fellows.aspx (last visited Feb. 24, 2012).

[3]The Regulatory Affairs Professional Development Framework offers a model for describing the basic body of knowledge and relevant skills of the RA profession across product lines, geographic locations and employer types at four major career stages. The skills, knowledge, and experience that I provide are reflected in this research-driven whitepaper.

was recognized in 2008 for my career accomplishments by induction to the Bossier High School Alumni Hall of Fame.

A copy of my current Curriculum Vitae is attached as Appendix A.

B. Methodology

I have been asked to address the actions of Ethicon, Inc., Ethicon Women's Health and Urology, a Division of Ethicon, Inc., Gynecare, and Johnson & Johnson (collectively referred to as Ethicon) in the context of the company's regulatory responsibilities as the manufacturer of the medical device GYNECARE Tension Free Vaginal Tape System (referred to as TVT™ Retropubic System, TVT or TVT Classic), indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. All of my opinions expressed in this Report are offered to a reasonable degree of scientific and professional certainty.

During the preparation of this Report, I reviewed, consulted, and relied upon the following categories of information, listings of which are provided in Appendix B:

a) Applicable statutes, regulations and guidance documents;
b) 510(k) Premarket Notifications, Numbers K974098 and K012628, and related Ethicon and FDA correspondence;
c) Other 510(k) Summaries relevant to the TVT regulatory history;
d) Other Ethicon documents of multiple types produced in this litigation;
e) Documents located by specifically directed independent on-line searches;
f) Relevant scientific and medical literature (See Appendix C);
g) Deposition transcripts of Dr. Axel Arnaud, Dr. Piet Hinoul, Dr. Martin Weisberg, Dr. David Robinson, Catherine Beath, Susan Lin, Gregory Jones, Daniel Smith, Boris Batke, Christophe Vailhe, Dr. Joerg Holste, and Daniel Burkley; Dan Lamont, Laura Angelini, and Bryan Lisa;
h) Ethicon website for Gynecare TVT™ Retropubic System; and
i) FDA website, including the searchable 510(k) database; the Manufacturer and User Facility Device Experience (MAUDE) Database for reports of serious adverse events; FDA's advisories and actions to address the safety issues associated with transvaginal mesh products for pelvic organ prolapse, e.g., FDA's 2008 *Public Health Notification*, 2011 *Safety Communication*, and 2011 Medical Devices Advisory Committee meeting of the Obstetrics and Gynecology Medical Devices Panel; Warning Letters.

A number of these documents are cited in footnotes throughout this Report as primary reference materials.

In reaching my opinions, based on my review, critical evaluation, synthesis, integration, and analysis of the body of relevant evidence, I brought to bear my educational background, professional training, and experience in the fields of regulatory affairs and medical product research and development, including nonclinical and clinical testing to determine medical

product safety and efficacy. I also drew upon the real world lessons learned from my industry experience.

The methodology I employed and level of scrutiny applied to the totality of the evidence in this matter and in the preparation of this Report are no different than those used in my practice over the course of my career as an expert in regulatory affairs and medical product research and development, including the testing and evaluation of medical product safety and efficacy, and as a researcher, educator, and scientist in general. Essentially, I conducted background research, constructed theories, tested those theories against the information I reviewed and the industry standards of which I am aware through my knowledge, experience, and training, analyzed my findings, and communicated my conclusions herein.

I conducted comprehensive observations and analysis of the totality of the categories of information listed above. I employed logical reasoning to my findings and formed conclusions, which are validated by information in the documentation and deposition records. I drew conclusions from my observations based on my extensive and specialized experience. . My opinions are grounded in well-established techniques, processes, and methods. They reflect practices commonly undertaken in the medical device industry within the context of the applicable federal regulatory scheme that informs and guides industry standards and conduct.

II. U.S. STATUTORY AND REGULATORY AUTHORITY: BASIS FOR OPINIONS

The purpose of this Section is to establish the regulatory and scientific foundation on which my professional opinions are based and set forth in this Report. Thus, I will provide a brief overview of FDA's authority to regulate medical devices, and the manufacturer's responsibility to comply with applicable regulations. I will describe device classifications and the corresponding premarket submissions required in order for a manufacturer to obtain FDA's authorization to sell a medical device in the U.S. I will complete this Section with a detailed explanation of a device manufacturer's postmarket responsibilities concerning (i) labeling and advertising and (ii) postmarket vigilance, or surveillance.

A. FDA Authority and Manufacturer Regulatory Compliance

The U.S. Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS) is responsible for regulatory oversight of the manufacture, sale, and distribution of medical devices in the United States under authority of the Federal Food, Drug, and Cosmetic Act (FDCA). Within the FDA, the Center for Devices and Radiological Health (CDRH) is the center that has the responsibility to develop and implement regulations for the purpose of protecting the public health in the field of medical devices. Ensuring optimum safety and device effectiveness, however, requires the cooperation of all stakeholders involved in the life cycle of a medical device: the manufacturer, FDA, and the end users. Each has a specific role to play in risk management. It is also important to remember that the FDA regulations are minimum standards, and where safety or effectiveness is an issue, the manufacturer bears the ultimate responsibility of ensuring the safety and effectiveness of its devices.

The medical device manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device.[4] The term "person" includes individual, partnership, corporation, and association.[5] Manufacture, preparation, propagation, compounding, assembly, or processing of a device means the making by chemical, physical, biological, or other procedures of any article that meets the definition of a device in Section 201(h) of the FDCA:[6] an article intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body but which does not achieve its primary intended purposes through chemical action and is not dependent upon being metabolized to achieve its primary intended purposes.

The FDA does not design and conduct either nonclinical or clinical studies to support device safety and effectiveness; it will advise on the adequacy of studies proposed by the manufacturer and then review the completed study results and other information submitted to FDA to determine if the materials submitted support the safety and effectiveness of the device sufficiently to clear or approve the device for sale for the requested indication(s) for use. Importantly, the FDA's capacity to monitor every single medical device, or drug/biologic, postmarketing is limited. There are more than 20,000 companies worldwide that produce over 80,000 brands and models of medical devices in the U.S. marketplace, according to CDRH.[7] That is why FDA depends on the cooperation and good faith of the device manufacturer to comply with FDA's regulatory decisions and applicable FDA regulations. It is the manufacturer's responsibility to ensure its devices are labeled and marketed in compliance with applicable FDA regulations.

While the FDA maintains a passive postmarketing surveillance system for safety concerns, the limitations of such a system underscore why the manufacturer is responsible for implementing a postmarket vigilance (surveillance) program. Specifically, the manufacturer must investigate and report to the FDA all serious or life-threatening adverse events about which it becomes aware if there is a reasonable suggestion that the manufacturer's device may have caused or contributed to such events. If the manufacturer becomes aware of the "need for remedial action from any information, including any trend analysis" in order "to prevent an unreasonable risk of substantial harm to the public health," the manufacturer must report such information to the FDA immediately (i.e., within five work days after becoming aware of the event).[8] The manufacturer must also maintain systems that ensure access to such adverse event information for timely follow-up and FDA inspection.[9]

In recent years, the FDA's authority and its capacity to discharge its responsibilities have been reviewed by independent agencies, including the Institute of Medicine and the Government Accountability Office (GAO). Summarily, these reports have recognized that FDA lacks the capacity to provide adequate oversight. While FDA continues efforts to address its increasingly

[4] 21 CFR § 820.3(o).
[5] Section 201(e) of the Federal Food, Drug, and Cosmetic Act (FDCA).
[6] 21 CFR § 807.3(d).
[7] AdvaMed (Advanced Medical Technology Association). The 510(k) Process: The Key to Effective Device Regulation, 8/19/08, p.2.
[8] 21 CFR § 803.53(a).
[9] 21 CFR § 803.17(b)(4).

complex public health mission of assuring medical product safety, effectiveness, and quality, the findings in these reports further emphasize why it is of critical importance for the device manufacturer to act in good faith at all times to ensure compliance with its responsibilities, as set forth in the applicable regulations, to prevent unnecessary risk to the public health.

The FDA provides multiple alternative avenues to medical device companies to assist them in interpreting any perceived grey areas in the regulations. Reasonably prudent medical device manufacturers avail themselves of these avenues provided by the FDA to ensure compliance, particularly when a question arises as to the proper course of regulatory action. These multiple alternative avenues include guidance documents and the ability to call the FDA, email the FDA, and meet with the FDA. In addition, reasonably prudent medical device manufacturers are always expected to err on the side of caution, i.e., regulatory compliance, when faced with any uncertainty or ambiguity in the regulations.

B. Device Classifications

FDA classifies medical devices into one of three regulatory classes based on the level of risk associated with use of the device and the level of control necessary to reasonably assure that the device is safe and effective for its intended use. Devices posing the lowest risk are placed in Class I and are subject to the least regulatory control. Class I devices, such as elastic bandages and tongue depressors, present minimal potential for harm to the user and are subject to the "General Controls" applicable to all medical devices. General Controls are the basic provisions of the 1976 Medical Device Amendments to the FDCA that provide the FDA with the means of regulating devices to ensure their safety and effectiveness. General Controls include provisions for adulteration, misbranding, establishment registration and device listing, premarket notification [510(k)], records and reports, and Good Manufacturing Practices/Quality System Regulation (QSR), among others.[10]

Class II devices pose incrementally greater risk such that the General Controls are not sufficient to provide reasonable assurance of safety and effectiveness. Class II devices are subject to "Special Controls" in addition to General Controls. Special Controls may include labeling requirements, performance standards, postmarket surveillance studies, or other controls the Agency deems necessary to provide reasonable assurance of the safety and effectiveness of the device. Ethicon's TVT System is a Class II device. Electrocardiographs and powered bone drills are other examples of Class II medical devices. Highest-risk devices, such as some implants and life-supporting devices, are placed in Class III and generally are subject to Premarket Approval (PMA), which is discussed below, and means that an application must be submitted to and approved by FDA before the device may be legally marketed.

C. The PreMarket Review Process: 510(k) vs. PMA

In general, unless exempt under FDA regulations, devices are subject to one of two types of FDA premarket review before they may be legally marketed in the United States. Class I and II devices subject to premarket review are required to obtain FDA clearance through the premarket notification, or 510(k) process; Class III devices are required to obtain FDA approval through the

[10] 21 CFR § 860.3; Device Advice – General Controls for Medical Devices, US FDA/CDRH.

more stringent PMA process. (There is a third but infrequently used alternative, the Product Development Protocol [PDP], which combines plans for an Investigational Device Exemption [IDE] to conduct a clinical trial.) Most Class I devices and a few Class II devices are exempt from the 510(k) requirements but are not exempt from other General Controls, which are discussed in Section II.B. above. All medical devices must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labeled, and have establishment registration and device listing forms on file with the FDA.[11]

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, i.e., substantially equivalent (SE), as a legally marketed device. Legally marketed devices, in this context, include any device that was legally marketed prior to May 28, 1976 (i.e., a preamendments device), for which a PMA is not required, and any device which has been found SE through the 510(k) process.[12] To support substantial equivalence claims, the device that is the subject of a 510(k) must be compared to one or more similar legally marketed devices, commonly referred to as "predicate(s)." A claim of substantial equivalence does not mean the new and predicate device(s) must be identical. SE is established with respect to intended use, design, materials, manufacturing process, performance, safety, effectiveness, labeling, standards, and other characteristics, as applicable. While clinical trials generally are not necessary for 510(k) submissions, FDA may require the conduct of clinical trials to substantiate the safety and effectiveness of a device in approximately 10-15% of cases and also may require postmarket surveillance to obtain 510(k) clearance.

In addition to the traditional method of demonstrating substantial equivalence under section 510(k) of the FDCA, there are two alternative approaches that may be used, under appropriate circumstances, to demonstrate substantial equivalence: (i) "Special 510(k): Device Modification" option, which utilizes certain aspects of the Quality System Regulation, and (ii) "Abbreviated 510(k)" option, which relies on the use of guidance documents, special controls, and recognized standards to facilitate 510(k) review. In accordance with the Quality System Regulation,[13] manufacturers must establish and follow a systematic set of pre-production design controls when initially designing medical devices or when making subsequent modifications to those designs. If a manufacturer is intending to modify its own legally marketed device and the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device, then summary information that results from the design control process can serve as the basis for 510(k) clearance, and the "Special 510(k): Device Modification" option may be utilized.[14]

Further, FDA has provided guidance to assist the medical device manufacturer to decide when a change to an existing device already in commercial distribution represents a significant change that requires a 510(k) premarket notification,[15] i.e., a change that could significantly affect the

[11] Device Advice – Class I/II Exemptions, US FDA/CDRH.
[12] 21 CFR § 807.92(a)(3).
[13] 21 CFR Part 820: Quality System Regulation.
[14] The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance, US FDA/CDRH, March 20, 1998.
[15] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997.

safety or effectiveness of the device or a major change in the intended use of the device.[16] "The type of modifications addressed in the draft guidance includes labeling changes, technology or performance specifications changes, and materials changes. When making the decision on whether to submit a 510(k), the manufacturer's basis for comparison of any changed device should be the device described by the cleared 510(k). The guidance includes a main flowchart to help manufacturers through the logic scheme necessary to arrive at a decision on when to submit a 510(k) for a change to an existing device. If a manufacturer's consideration of all proposed changes results in a decision that a 510(k) submission is not required, they should document the basis for the decision, including the application of the flowchart model, along with the necessary records of the validation of changes to the device. In those circumstances where the proposed change is not addressed in the flowchart or in a device-specific guidance document, manufacturers are encouraged to contact the Office of Device Evaluation in CDRH to find out whether other, specific guidance exists or if additional help is available."[17]

Following submission of a 510(k), the subject device may not be marketed in the U.S. until the 510(k) applicant receives a letter (i.e., order) declaring the device substantially equivalent, thereby "clearing" the device for marketing. This is an important distinction in that the device is not technically "approved" by the FDA as with a PMA but instead is said to be cleared, or 510(k)-cleared, for marketing. A substantially equivalent determination means that the new device is at least as safe and effective as the predicate(s), specifically, that the new device has:

(1) The same intended use and the same technological characteristics as the predicate(s);
or
(2) The same intended use and different technological characteristics, and the information submitted to FDA:
   a. Does not raise new questions of safety and effectiveness; and
   b. Demonstrates that the new device is at least as safe and effective as the predicate device(s).

Technically, by regulation[18] the FDA has 90 days to review the 510(k) and issue a SE or not substantially equivalent (NSE) determination. If the FDA determines that a device is NSE (novel), it is considered Class III and will require a PMA prior to marketing. At this point, the 510(k) sponsor has the following options: (1) cease plans to market the device; (2) request reclassification; (3) submit a request for evaluation of the automatic Class III designation; (4) present new evidence (data) in support of a 510(k) clearance; or (5) proceed to develop the device through the PMA route. A Class II device that is introduced into commercial distribution without a required 510(k) clearance is considered "adulterated" and "misbranded" and subject to regulatory sanctions.

[16] 21 CFR § 807.81(a)(3).
[17] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997.
[18] 21 CFR Part 807.

A PMA application is generally considered to be a more rigorous process than the 510(k) and is analogous to the New Drug Application (NDA) or Biologics License Application (BLA) that must be submitted for review and approval prior to marketing for drugs and biologics, respectively. The PMA is generally required for Class III devices that are determined to be either novel or that pose a significant risk of illness or injury.[19] Approval hinges on a demonstration of safety and effectiveness through the presentation of valid scientific evidence. Most often, this path requires the conduct of prospective controlled clinical trials conducted in accordance with the strict Good Clinical Practice (GCP) standards established by the FDA and the International Community. By regulation[20], the FDA has 180 days to review a PMA and issue a decision concerning approval of the application. In general, a Class III device that is introduced into commercial distribution without an approved PMA is considered "adulterated" and "misbranded" and subject to regulatory sanctions.

D. Determination of Substantial Equivalency

Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate that a device is substantially equivalent to a predicate device, the device manufacturer is supposed to rely upon only valid scientific evidence.. Valid scientific evidence may include evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Note that the 510(k) process only requires that a new device demonstrate "substantial equivalence" to a previously cleared device or device marketed before 1976 ("predicate" device). Products cleared via the 510(k) process are not required to demonstrate safety and effectiveness, but substantial equivalence is taken to mean that the new device is "at least as safe and effective" as the predicate.[21] This is in contrast to the Premarket Approval process, which is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

E. Device Label, Labeling, Advertising, and Misbranding

The General Controls applicable to all devices include provisions for proper labeling and misbranding. The Federal Food, Drug and Cosmetic Act (FDCA) is the law that applies to manufacturers for labeling and advertising violations concerning products it regulates. The following are standard terms and principles used within the medical device industry and applied in industry practice. These form the basic building blocks for industry to establish governing standards of practice and are built upon through application of experience, training, and as circumstances dictate.

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[19] 21 CFR Part 814.
[20] 21 CFR § 814.40.
[21] Medical Devices: How to Market Your Device, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/

1. Applicable Definitions

The laws enacted by the U.S. Congress concerning products regulated by the FDA are implemented by the FDA as enforceable regulations. Together, these laws and implementing regulations define the terms that are applicable to device labeling, advertising, and misbranding. Some of the terms that are significant for purposes of this Report include the following.

1.1 Label: Section 201(k) [21 U.S.C. 321(k)] of the FDCA defines "label" as a:

> "display of written, printed, or graphic matter upon the immediate container of any article..."

The term "immediate container" does not include package liners. Any word, statement, or other information appearing on the immediate container must also appear "on the outside container or wrapper, if any there be, of the retail package of such article," or must be "easily legible through the outside container or wrapper."

1.2 Labeling: Section 201(m) [21 U.S.C. 321(m)] of the FDCA defines "labeling" as:

> "all labels and other written, printed, or graphic matter
> (1) upon any article or any of its containers or wrappers, or
> (2) accompanying such article" at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.

The term "accompanying" is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. "Accompanying" also includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.[22] Training and instructional videos are considered labeling. Websites are also considered under this broad definition of labeling, and the statements a manufacturer makes about its product on websites are regulated as labeling and must be truthful and accurate.

1.3 Indications for Use

The general statement of "Indications for Use" identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.[23]

1.4 Intended Uses

The term "intended uses" refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the

[22] Device Advice – Labeling Requirements, US FDA/CDRH.
[23] Device Labeling Guidance 3/8/91 (G91-1) – Blue Book Memo.

circumstances surrounding the distribution of the device. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such representatives. It may be shown by the offering or the using of the device, with the knowledge of such persons or their representatives, for a purpose for which it is neither labeled nor advertised.[24]

1.5 Contraindications

This term refers to situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Known hazards and not theoretical possibilities are to be listed as contraindications. For example, if hypersensitivity to an ingredient in the device has not been demonstrated, it should not be listed as a contraindication.[25] Furthermore, should a medical device manufacturer have information that its medical device does not perform well in certain patient populations, it should list that information in the contraindications section.

1.6 Directions for Use (DFU) (or Instructions for Use [IFU])

This means the providing of directions to the practitioner or layman (e.g., patient), as appropriate, so that s/he can use the device safely and for the purposes for which it is intended. "Directions for Use" also include indications for use and appropriate contraindications, warnings, precautions, and adverse reaction information. Directions for Use requirements applicable to prescription devices appear throughout 21 CFR Part 801.[26]

1.7 Fair Balance

For advertising and promotional materials, this term means that advertisements must communicate fairly and in a balanced manner information relating to side effects and contraindications and information relating to effectiveness of the product.[27] In other words, information about side effects and contraindications must be comparable in depth and detail with claims for safety and effectiveness.

1.8 Prescription Device

By definition under 21 CFR § 801.109, this is a device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe except under the supervision of a practitioner licensed by law to direct the use of the device, and hence for which "adequate directions for use"[28] cannot be prepared.

[24] 21 CFR § 801.4; Device Labeling Guidance 3/8/91 (G91-1) – Blue Book Memo.
[25] *Id.*
[26] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[27] 21 CFR §§ 202.1(e)(5) and (6).
[28] 21 CFR § 801.5.

2. ***General Device Labeling: 21 CFR Part 801***

General labeling requirements for medical devices have been established in 21 CFR Part 801. Guidance on "Indications for Use," "Contraindications," "Warnings," "Precautions," and "Adverse Reactions" paraphrase applicable provisions in the labeling requirements for prescription drugs.[29]

A premarket notification must normally only contain proposed labeling sufficient to describe the device's intended use, as discussed in the "Blue Book" 510(k) Memorandum #K86-3 dated June 30, 1986.[30] Accordingly, a 510(k) finding of substantial equivalence does not connote approval of the proposed labeling. However, in the case of devices with special labeling requirements and devices for which inclusion of specific directions for use, contraindications, warnings, etc., in the labeling may be critical to a finding of equivalence, CDRH's Office of Device Evaluation (ODE) 510(k) labeling review includes an evaluation of compliance of the proposed labeling or portions thereof, as appropriate.

In contrast, specific labeling is approved as part of a PMA. While FDA will approve a PMA on the basis of draft final labeling if the only deficiencies concern editorial or similar minor deficiencies in the draft final labeling, PMA approval depends on incorporation of the specific labeling changes exactly as directed and the manufacturer is required to submit to FDA a copy of the final printed labeling before marketing.[31] Labeling changes that affect the safety or effectiveness of a device require a PMA supplement and can be done without FDA approval via a Special PMA Supplement only when such modifications are based on newly acquired information and evidence of a causal relationship between the product and a safety signal. New information "must reveal risks of a different type or greater severity or frequency than previously included in submissions."[32,33] Importantly, routine review of patient labeling for all original PMAs and panel-track supplements will be conducted by the FDA Division of Device User Programs and Systems Analysis (DDUPSA) when human factors for the usability of the device need to be considered.[34]

3. ***Patient Labeling***

FDA issued a guidance in April 2001, titled "Guidance on Medical Device Patient Labeling," to assist manufacturers in their development and FDA reviewers in their review and evaluation of patient labeling, "to help make it understandable to and usable by patients," and lay caregivers as applicable.[35] Medical device patient labeling is any information associated with a device

[29] 21 CFR Part 201; Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[30] Guidance on the CDRH Premarket Notification Review Program 6/30/86 [K86-3]: 510(k) Memorandum #K86-3.
[31] FDA Device Advice: Device Regulation and Guidance. PMA Labeling http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050390.htm.
[32] 21 CFR § 814.39 PMA Supplements.
[33] Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision. Dec 11, 2008 http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089274.htm#4e.
[34] FDA Memorandum of Understanding Regarding Patient Labeling Review (Blue Book Memo #69-3).
[35] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.

targeted to the patient or lay caregiver. It is intended to help assure that the device is used safely and effectively. This labeling may pertain to therapeutic, restorative, diagnostic, or cosmetic devices.

Medical device patient labeling is supplied in many formats, **for example, as patient brochures,** patient leaflets, user manuals, and videotapes.[36] [Emphasis added] This labeling is intended to be supplied, or given to and used by patients or their lay caregivers with or without accompanying professional counseling. **Medical device patient labeling may accompany devices intended solely for physicians to operate**, devices for both physicians and patients or lay caregivers to operate, and devices operated solely by patients or their lay caregivers. [Emphasis added.]

Medical device patient labeling should be supplied whenever it can benefit patients or lay caregivers by increasing their knowledge about the device. The informational needs of the target audience should be known in order to determine if patient labeling is necessary, e.g., whether patients need or want specific information, whether there is something unique about the device that needs to be explained to the patient, and whether patients already know the information.

Providing risk/benefit information is important when patients or lay caregivers need to:

- select among similar devices or device procedures;
- be involved in deciding whether to have a procedure involving the device; and/or
- understand the effect or influence of the device on the patient or others.

Risk/benefit information is particularly pertinent to patients considering the implantation of synthetic, biosynthetic or biological meshes for vaginal prolapse, versus non-mesh repair.

4. The Meaning of Intended Use

To determine whether or not a new device has the same intended use as a predicate device, CDRH assesses any difference in label indications based on the safety and effectiveness questions they may raise. As described in Section II.C., "same intended use" is a key determinant in assessment of substantial equivalence. CDRH considers such points as condition or disease to be treated or parts of the body or types of tissue involved, etc. If a new device is determined to have the same intended use, CDRH may then proceed to determine whether or not it is substantially equivalent. Devices that do not have the same intended use cannot be substantially equivalent.[37]

5. Promotion and Intended Use

Products are cleared or approved for certain intended uses. Change in Intended Use may require a new clearance or approval. New Intended Use can be created by:

[36] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[37] Guidance on the CDRH Premarket Notification Review Program 6/30/86 [K86-3]: 510(k) Memorandum #K86-3.

(1) Labeling, advertising, or promotional claims;
(2) Oral statements;
(3) Manifestations of objective intent;[38]
(4) Expressions;
(5) Circumstances of distribution; and
(6) Offering with knowledge of use.[39]

6. Labeling and Advertising (General Device Labeling: 21 CFR Part 801)

The distinction between labeling and advertising, both of which draw attention to the article to be sold, is often superficial or nebulous. Both are used for a similar purpose, i.e., to provide information about the product. Thus, according to an appellate court decision, "[m]ost, if not all, labeling is advertising. The term 'labeling' is defined in the FDCA as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."[40]

While advertising and promotion are not defined in the FDCA and FDA regulations for medical devices, FDA interprets any activity used by the sponsor to create an interest in the company's products, including the Internet, as advertising.[41] It is noteworthy that FDA has defined prescription-drug advertising as including "advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems."[42]

Jurisdiction over medical device advertising is split between the FDA and the Federal Trade Commission (FTC). The FTC has primary oversight responsibility for the advertising of non-restricted devices. The FTC prohibits advertising that is false and misleading and requires substantiation of all claims that are made in advertisements.[43] With regard to the advertising of medical devices, the FTC has defined substantiation as requiring balanced, scientific evidence in the form of well-controlled clinical studies.

Except in extraordinary circumstances, FDA cannot require prior approval of the content of any advertisement except in the case of any printed matter which FDA determines to be labeling as defined in Section 201(m) of the FDCA.[44] In practice, many items that could meet the definition of "advertising" also meet the definition of "labeling" and are regulated by FDA as labeling.

7. Misbranding

Section 502 of the FDCA (21 U.S.C. § 352) contains provisions on misbranding and false or misleading labeling. A device is misbranded if:

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[38] 21 CFR §§ 201.128, 801.4.
[39] 21 CFR § 801.4.
[40] *United States v. Research Laboratories, Inc.*, 126 F.2d 42, 45 (9th Cir. 1942), *cert. denied*, 317 US 656 (1942).
[41] FDA Docket No. 2005N-0354.
[42] 21 CFR § 202(l)(1).
[43] 15 U.S.C. § 45.
[44] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.

(1) Its labeling is false or misleading in any particular;[45]
(2) Its advertising is false or misleading in any particular;[46]
(3) It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling;[47]
(4) Its labeling does not bear adequate warnings;[48]
(5) There is a failure to furnish any materials or information requested by or under Section 519 of the FDCA on reports and records;[49] and
(6) There is a failure to have a necessary 510(k) clearance.[50]

Pursuant to the FDCA § 201(n), a device is misbranded when there is a failure to reveal material facts.

In summary, prescription medical devices such as Ethicon's TVT System are misbranded if their labels do not bear information for use including indications, effects, routes, methods, frequency and duration of administration (as applicable), and any relevant hazards, contraindications, side effects and precautions under which practitioners licensed by law to administer the devices can use them safely and for the purpose for which they are intended, including all purposes for which they are advertised or represented,[51] or if there is a failure to obtain the necessary 510(k) clearance.

A medical device may be misbranded not only if the actual label contains false or misleading representations, but also if the device's advertising fails to reveal facts material to the representations made or consequences that may result from the use of the product under the conditions of use prescribed in the labeling or advertising or under such conditions of use as are customary or usual.[52] Labeling and advertising must therefore present a fair balance of information relating to the side effects and effectiveness of the product.

8. False or Misleading Labeling

The phrase "false or misleading" is not confined in meaning to untrue, forged, fraudulent, or deceptive. The word "misleading" in the FDCA means that labeling is deceptive if it creates or leads to a false impression in the mind of the reader. A "false impression" may result not only from a false deceptive statement, but may also be instilled in the mind of the consumer by ambiguity, misdirection, or failure to inform the consumer of facts that are relevant to those statements actually made**. In other words, the label that remains silent as to certain consequences may be as deceptive as the label that contains extravagant claims.**[53]

[45] FDCA § 502(a).
[46] FDCA § 502(j).
[47] 21 U.S.C. § 352.
[48] FDCA § 502(f)(2).
[49] FDCA § 502(t).
[50] FDCA § 502(o).
[51] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[52] 21 U.S.C. § 321(n).
[53] Device Advice – Labeling Requirements: Misbranding, US FDA/CDRH.

Examples of false or misleading labeling include, among others:

(1) Unsubstantiated claims of therapeutic value;
(2) Expression of opinion or subjective statements; and
(3) Failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion.[54]

9. Warnings

Product labeling is a primary cornerstone of managing product safety, because communication of serious risk is critical to prevent or mitigate product risk. Thus, labeling content, including warning statements when required to protect users, is a key factor in determining whether there is reasonable assurance that a device is safe and effective for its intended use.

Warning statements on "Instructions for Use" should be delineated by underlining, bold print, boxing, etc. The purpose of "Warnings" is to describe serious adverse reactions and potential safety hazards, the limitations of device use due to such concerns, and steps that should be taken if they occur. A causal relationship need not have been proved.

As discussed in FDA's guidance document titled "Guidance on Medical Device Patient Labeling," there are four elements generally recognized by the courts and research as necessary for an effective warning:

(1) Signal word, i.e., WARNING;
(2) Hazard avoidance directive to give clear instructions to the user on how to avoid the hazard;
(3) Clear statement of the nature of the hazard associated with the warning that characterizes the severity and the likelihood; and
(4) Consequences, specifying the serious adverse events, potential safety hazards and limitations in device use that result if users do not follow instructions.[55]

In other words, for patient labeling, warnings must be set forth in plain language in a manner designed to be understood by the lay person without a medical background. A warning is insufficient if the reader does not understand or appreciate the consequences of failure to comply with the Warning. Hazard alert research has shown that giving a clear idea of the risk has a significant effect on readers.[56]

10. Dear Doctor, or Dear Health Care Professional, Letters

The Center for Drug Evaluation and Research, Manual of Policies and Procedures MAPP 6020.10 is entitled "Dear Health Care Professional" (DHCP) letters and applies specifically to those DHCP letters that concern information about significant hazard to health and/or important

[54] Device Advice – Labeling Requirements: Misbranding, US FDA/CDRH.
[55] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[56] *Id.*

changes in package labeling.[57] FDA issued a new Draft Guidance in November 2010 titled "Dear Health Care Provider Letters: Improving Communication of Important Safety Information."[58] This Guidance provides recommendations to industry and FDA staff on the content and format of DHCP letters, which are correspondence, usually in the form of a mass mailing from the manufacturer or distributor, to alert physicians and other health care providers responsible for patient care about important new information regarding a human drug or biologic (hereafter "drug").

While the cited policy and guidance are designed for drugs, the policies discussed are equally applicable for medical devices. For example, the overall concepts of the July 2007 Guidance for Industry and Staff titled "Writing *Dear Doctor* Letters for Recalls of Implantable Cardioverter Defibrillators (ICDs)"[59] are reflective of the general policies discussed in the referenced drug policy and guidance documents. Moreover, this guidance states that some of its concepts may be appropriately applied to other implanted devices and, importantly, that the recommendations in the guidance draw from "FDA's own research, risk communication principles, and other efforts to standardize the information in *Dear Doctor* letters."

The drug policy makes clear that the FDA may or may not be involved in reviewing DHCP letters before they are mailed. In other words, a company may send out a Dear Health Care Professional letter without approval from the FDA in the event that the company believes that a significant health hazard may endanger patients or that an important labeling change needs to be seen by physicians. Nevertheless, as stated in the new Draft Guidance, FDA believes that effective communication of important new information in DHCP letters can best be accomplished if FDA and the manufacturer work together.

F. Quality System Regulation (QSR) and Design Controls

The 1976 Medical Device Amendments to the FDCA provided for FDA to prescribe Good Manufacturing Practice (GMP) requirements to ensure that medical devices are consistently manufactured according to written specifications and are safe and effective for their intended use. The original GMP regulation became effective on December 18, 1978. In 1990, FDA initiated efforts to revise the regulation due to a large number of device failures and recalls resulting from design defects. The Safe Medical Devices Act of 1990 (SMDA) amended Section 520(f) of the FDCA, providing FDA with the authority to require design controls as part of the GMP regulation. On October 7, 1996, FDA revised the GMP regulation with publication of the Quality System Regulation (QSR), which became effective June 1, 1997. The QSR[60] requires medical device manufacturers to implement and comply with procedures covering the following broad areas: quality system requirements; design controls; document controls; purchasing controls; identification and traceability; production and process controls; acceptance activities; nonconforming product; corrective and preventive action; labeling and package

[57] Manual of Policies and Procedures MAPP 6020.10: NDAs: "Dear Health care Professional" Letters, effective date 7/2/03, issued by CDER, FDA.
[58] Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of Important Safety Information, issued November 2010, CDER/CBER, FDA.
[59] Guidance for Industry and FDA Staff: Writing *Dear Doctor* Letters for Recalls of Implantable Cardioverter Defibrillators (ICDs), issued July 19, 2007 by CDRH, FDA.
[60] 21 CFR Part 820.

control; handling, storage, distribution, and installation; records; servicing; and statistical techniques. Of particular importance to the subject matter of this Report and thus discussed below are the quality system requirements, design controls, and complaint files (latter addressed in the QSR under Subpart M, Records).

1. Quality System Requirements

The manufacturer is required to establish and maintain a quality system appropriate for the medical devices it designs and manufactures.[61] It is the responsibility of executive management to establish the quality policy and commitment to achieving quality at all levels of the organization.[62] Among management's other responsibilities is the requirement to establish a quality plan that defines the practices, resources, and activities necessary to meet quality requirements.[63] The suitability and effectiveness of the quality system must be reviewed frequently enough to ensure that the company's quality system is in compliance with QSR requirements. Effectiveness of the quality system is required to be monitored through the conduct of periodic audits, the results of which must be reviewed by management with executive responsibility.[64] Further, the QSR emphasizes that appropriately educated and adequately trained and experienced personnel are necessary to assure that an effective quality system is not only established but maintained.[65]

2. Design Controls

Design control requirements apply to all Class II and Class III medical devices and certain Class I devices.[66] The purpose of the QSR design control requirements is to ensure that the design of a medical device is monitored and controlled such that all specified design requirements are achieved. The phases of design controls[67] include the following:

- Design input: physical and performance requirements of the device for its intended use, including the needs of the user and patient;
- Design output: results of the design effort at each design phase and at the end of design development, including the device, labeling and packaging, associated specifications and drawings, and production and quality assurance specifications and procedures;
- Design review: conduct of formal, documented reviews of design results at appropriate intervals during device design development;
- Design verification: testing to verify the design output meets design input requirements;
- Design validation: (i) testing device performance under actual or simulated conditions of use, in order to establish by objective evidence that device specifications satisfy user needs and intended use(s); (ii) includes risk analysis, where appropriate;
- Design transfer: transition of device design from research and development to production specifications;

[61] 21 CFR § 820.5.
[62] 21 CFR § 820.20(a).
[63] 21 CFR § 820.20(d).
[64] 21 CFR § 820.22.
[65] 21 CFR § 820.25.
[66] 21 CFR 820.30(a).
[67] 21 CFR 820.30(c) through (i).

- Changes in device design: procedures for the identification, documentation, validation or where appropriate verification, review and approval of design changes before implementation.

3. Complaint Files

Device manufacturers are required to establish and maintain procedures for receiving, reviewing, and evaluating complaints. A "complaint" is defined as "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution."[68] Complaint handling procedures must ensure that all complaints are processed in a uniform and timely manner, that oral complaints are documented upon receipt, and that complaints are evaluated to determine whether the complaint represents an event that is required to be reported to FDA as a Medical Device Report. Any complaint that is an MDR-reportable event must be promptly reviewed, evaluated, and investigated.[69] Note that Medical Device Reporting requirements are discussed below in Section II.G.

Notably, all complaints must be reviewed and evaluated to determine if an investigation is necessary. If an investigation is not done, the reason it was not done and the name of the individual responsible for the decision not to investigate must be maintained in the complaint files. Any complaint involving the possible failure of a device, its labeling or packaging to meet specifications must be reviewed, evaluated, and investigated, unless investigation has already been done for a similar complaint and another investigation is not necessary.[70]

G. Manufacturer Serious Adverse Event Reporting Requirements

1. Historical Perspective

Since 1984, domestic manufacturers of medical devices have been required to report to the FDA all device-related deaths, serious injuries, and certain malfunctions. The statutory authority for the Medical Device Reporting (MDR) regulation is Section 519(a) of the Federal Food Drug & Cosmetic Act (FDCA). On September 14, 1984 (49 FR 36326), FDA issued Medical Device Reporting (MDR) regulations for manufacturers and importers under the FDCA and the Medical Device Amendments of 1976 (Public Law 94-295). To correct weaknesses noted in the 1976 amendments and to better protect the public health, Congress enacted the Safe Medical Devices Act of 1990 (SMDA) (Public Law 101-629). SMDA imposed significant new reporting requirements on the medical device industry, including user facilities and distributors of medical devices. To implement SMDA and changes mandated by the Medical Device Amendments of 1992 (Public Law 102-112) (amending certain provisions, Section 519 of the FDCA, relating to reporting of adverse events), FDA published the final MDR regulation for user facilities and manufacturers in the Federal Register on December 11, 1995. The new MDR regulation became effective on July 31, 1996.

[68] 21 CFR § 820.3(b).
[69] 21 CFR § 820.198.
[70] *Id.*

The FDA Modernization Act of 1997 (FDAMA) (Public Law 105-115) was signed on November 21, 1997, and FDAMA changes to medical device adverse event reporting (MDR) became effective on February 19, 1998. On January 26, 2000, changes to the implementing regulations, 21 CFR Parts 803 and 804, were published in the Federal Register to reflect these amendments in the FDCA. Also, Part 804, Medical Device Distributor Reporting, was removed. The MDR Rule changes became effective March 27, 2000.

2. Postmarket Vigilance/Surveillance – Medical Device Reporting (MDR) Regulation: 21 CFR Part 803

The purpose of Medical Device Reporting is to protect the public health by ensuring that devices are not adulterated or misbranded and are safe and effective for their intended use. The MDR regulation provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events in order that safety problems may be detected and corrected in a timely manner. While the requirements of the regulation can be enforced through legal sanctions authorized by the FDCA, accomplishing the objectives of the regulation is dependent on the compliance and cooperation of manufacturers and other affected entities such as user facilities, importers, and distributors.

Reporting device problems to the FDA is a critical communication link to ensure the safety and effectiveness of marketed medical devices. FDA continually evaluates the Manufacturer and User Facility Device Experience Database (MAUDE), which includes reports of adverse events involving medical devices, to detect potential hazards, or safety signals. The sooner the FDA learns about a problem, the sooner the Agency can take action to evaluate actual or potential risk and ensure that any necessary corrective action is initiated to protect patient safety. Sometimes a single report can initiate this action.[71]

2.1 Applicable Definitions

The FDA defines the terms that are used in the MDR regulation. Some of the terms that are significant for purposes of this Report include:

2.1.1 *MDR reportable event (or reportable event)*: An event that user facilities (e.g., hospital, ambulatory surgical facility, outpatient treatment facility) become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or an event that manufacturers become aware of that reasonably suggests that one of their marketed devices:

i. May have caused or contributed to a death or serious injury; or
ii. Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

[71] Improving Patient Care by Reporting Problems with Medical Devices. *A MedWatch Continuing Education Article*. Uniformed Services University of the Health Sciences and FDA. September 1997.

2.1.2 *Malfunction* means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed, as defined in 21 CFR § 801.4.

2.1.3 *Become aware* means that an employee of the manufacturer has acquired information that reasonably suggests a reportable adverse event has occurred.

1) For an event that is required to be reported within 30 calendar days, a manufacturer is considered to have become aware of the event when any of its employees becomes aware of the reportable event.
2) For an event reportable within 5 work days, the manufacturer is considered to have become aware of the event when any of its employees with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or whose duties relate to the collection and reporting of adverse events, becomes aware, from any information, including any trend analysis, that a reportable MDR event or events necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health.

2.1.4 *Reasonably suggests* means any information, including professional, scientific, or medical facts, observations, or opinions, that may reasonably suggest that a device has caused or may have caused or contributed to a MDR reportable event.

2.1.5. *Caused or contributed* means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error.

2.1.6. *Serious injury* means an injury or illness that:

1) Is life-threatening;
2) Results in permanent impairment of a body function or permanent damage to a body structure; or
3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

2.1.7 *Permanent* means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

2.1.8 *"*The term '*user error*' means any error made by the person using the device. A user error may be the sole cause or merely contribute to a reportable event. As with the 1984 regulation, there is the requirement for reports of certain adverse device events caused by user error. For example, device injuries attributed to user error may show that the device is misbranded within the meaning of section 502(f) of the FD&C Act [21 U.S.C. 352(f)] in that the

> device fails to bear adequate directions for use or adequate warnings. Reports of adverse events that result from user error may alert FDA to the need for improved labeling to prevent future injuries. (Refer to the FR preamble, page 63583, Final Rule, December 11, 1995.)"[72]

With these definitions in place, I will now address the manufacturer reporting requirements for the investigation, evaluation and reporting of serious adverse events.

3. Overview of Manufacturer Reporting Requirements

Part 803 of the Code of Federal Regulations Title 21 (21 CFR Part 803) is the implementing regulation for Medical Device Reporting. This Part establishes the requirements for medical device reporting for medical device manufacturers, importers, user facilities, and distributors. Regulations from this Part that are applicable to my analysis and professional opinions herein include the following:

(1) **Deaths and serious injuries that a manufacturer's device has or may have caused or contributed to must be reported to the FDA**;
(2) **Certain device malfunctions must also be reported**;
(3) The device manufacturer is required to establish and maintain adverse event files;
(4) **The device manufacturer is required to submit supplemental/follow-up reports when new (required) information is obtained that was not available when the initial Medical Device Report was submitted to FDA.**

4. Reporting of Adverse Events

A manufacturer is required to investigate, evaluate and submit reports of adverse events to the FDA pursuant to 21 CFR § 803.10(c); § 803.20(a), (b)(3); §803.50(a), (b); §803.52; §803.53; §803.56.

4.1 30-Day Reports

A manufacturer must submit reports of individual adverse events no later than 30 calendar days after the day that the manufacturer becomes aware of information from any source that reasonably suggests that a device may have caused or contributed to a death, serious injury, or a malfunction that, should it recur with the device in question or a similar device, would be likely to cause or contribute to a death or serious injury.[73]

4.2 5-Day Reports

In the case of a reportable event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health, the manufacturer must submit reports of individual adverse events no later than five (5) work days after the day the manufacturer becomes aware of the

[72] Medical Device Reporting for Manufacturers, Prepared by Division of Small Manufacturers Assistance Office of Communication, Education, and Radiation Programs, FDA CDRH, March 1997.
[73] 21 CFR § 803.10(c)(1); § 803.20(b)(3); § 803.50(a).

event. The manufacturer may become aware of the need for remedial action from any information, including any trend analysis.

Additionally, the FDA may make a written request for the submission of a 5-day report. In such case, the manufacturer must submit, without further requests, a 5-day report for all subsequent events of the same nature that involve substantially similar devices for the time period specified in the written request, which time period may be extended if FDA determines it is in the interest of the public health.[74]

4.3 Mandatory Reporting Information Requirements

The manufacturer must submit such mandatory reports using the FDA Form 3500A.[75] On this form, the manufacturer must provide all information required that is reasonably known to the manufacturer.

4.3.1 *Reasonably known* is considered to include the following information:

a) Any information that the manufacturer can obtain by contacting a user facility or other initial reporter;

b) Any information in the manufacturer's possession;

c) Any information that the manufacturer can obtain by analysis, testing, or other evaluation of the device.[76]

4.3.2 The manufacturer is responsible for obtaining and submitting to FDA information that is incomplete or missing from reports submitted by user facilities and other initial reporters.[77]

4.3.3 The manufacturer is responsible for conducting an investigation of each event and evaluating the cause of the event. If the manufacturer cannot submit complete information on a report, it must provide a statement explaining why this information was incomplete and the steps taken to obtain the information.[78]

4.3.4 If the manufacturer later obtains any required information that was not available at the time the initial Medical Device Report was filed, it must submit this information in a supplemental report.[79]

5. When is a Manufacturer Excused from Submitting an MDR?

A manufacturer does not have to report an adverse event if it has information that would lead a person who is qualified to make a medical judgment to reasonably conclude that a device did not cause or contribute to a death or serious injury.[80] Persons qualified to make a medical

[74] 21 CFR § 803.10(c)(2); § 803.20(b)(3); § 803.53.
[75] 21 CFR § 803.20(a).
[76] 21 CFR § 803.50(b)(1).
[77] 21 CFR § 803.50(b)(2).
[78] 21 CFR § 803.50(b)(3).
[79] *Id.*
[80] 21 CFR § 803.20(c)(2).

judgment include physicians, nurses, risk managers, and biomedical engineers. The manufacturer must keep in its MDR event files the information that the qualified person used to determine whether or not a device-related event was reportable.

A manufacturer is not required to submit a Medical Device Report if it determines that the information received is erroneous in that a device-related adverse event did not occur.[81] The manufacturer must retain documentation of such report in its MDR files for the time periods specified below under "Records Retention."[82]

When a manufacturer receives reportable event information for a device it does not manufacture, it is not required to submit a Medical Device Report, but the manufacturer must forward this information to the FDA with a cover letter explaining that it did not manufacture the device in question.[83]

6. The Submission of a MDR is Not an Admission of a Causal or Contributory Relationship

21 CFR § 803.16 makes clear that the manufacturer's submission of a MDR or release of that report by FDA is not necessarily an admission that the device, or the manufacturer or its employees, caused or contributed to the reportable event. The manufacturer does not have to admit and may deny that the report or information submitted under 21 CFR Part 803 constitutes an admission that the device, the manufacturer or its employees, caused or contributed to the reportable event. This regulation underscores the purpose of Medical Device Reporting, even when the manufacturer is in doubt that its device caused or contributed to a reportable event, i.e., to ensure that signals are not overlooked but can be identified and acted upon by the company and the FDA in a timely manner.

7. Requirements for Written MDR Procedures and Recordkeeping

7.1 Standardized Procedures

The manufacturer must develop, maintain, and implement written MDR procedures to identify, communicate, and evaluate adverse events. There must be a standardized review process for determining when an event meets the criteria for reporting under 21 CFR Part 803, and the information must be submitted to the FDA timely. Records must be maintained for all information that was evaluated to determine if an adverse event was reportable, and all Medical Device Reports and information submitted to FDA must be maintained. The company must have systems that ensure timely access to these records for follow-up and inspection by FDA.[84]

[81] 21 CFR § 803.22(b)(1).
[82] 21 CFR § 803.18(c).
[83] 21 CFR § 803.22(b)(2).
[84] 21 CFR § 803.17.

7.2 Establishing and Maintaining MDR Event Files

The manufacturer of a medical device is required to establish and maintain MDR event files. All MDR event files must be clearly identified and maintained to facilitate timely access.[85]

"MDR event files" are written or electronic files and must contain:

1) Information in the manufacturer's possession or references to information related to the adverse event, including all documentation of deliberations and decision-making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable under 21 CFR Part 803; and
2) Copies of all MDR forms, as required by 21 CFR Part 803, and other information related to the event that the manufacturer submitted to FDA.

A manufacturer may maintain MDR event files as part of its complaint file, under 21 CFR Part 820, if the MDR reportable events are prominently identified as such.

7.3 Records Retention

The medical device manufacturer must retain a MDR event file relating to an adverse event for a period of two (2) years from the date of the event or a period of time equivalent to the expected life of the device, whichever is greater.[86] Accordingly, in the case of a permanently implantable medical device, the regulations require the manufacturer to maintain MDR event files indefinitely.

8. Global Harmonization Task Force (GHTF) Guidances: Postmarket Vigilance

The Global Harmonization Task Force (GHTF)[87] was conceived in 1992 to address the growing need for international harmonization in the regulation of medical devices, with two principal aims: (i) enhancing patient safety and (ii) increasing access to safe, effective, and clinically beneficial medical technologies worldwide. Note that GHTF was disbanded and transitioned its unfinished work to its successor organization in 2012: IMDRF, International Medical Device Regulators Forum. During its approximately 20-year existence, GHTF was a partnership between regulatory authorities and the regulated medical device industry and was comprised of five Founding Members: United States, European Union, Canada, Australia, and Japan. Beginning in 2006, membership expanded to include three Liaison Body members: International Organization for Standardization (ISO), International Electrotechnical Commission (IEC), and Asian Harmonization Working Party (AHWP). A primary purpose of the GHTF was to encourage convergence in regulatory practices related to ensuring the safety as well as the effectiveness/performance and quality of medical devices. This was accomplished through the development and dissemination of harmonized guidance documents concerning basic regulatory practices. These documents were developed by different GHTF

[85] 21 CFR § 803.17.
[86] 21 CFR § 803.18(c).
[87] Global Harmonization Task Force Website: http://www.ghtf.org/.

Study Groups and provide a model for the regulation of medical devices and adoption/implementation by national regulatory authorities.

The GHTF Study Group 2 (SG2) was responsible for developing guidance documents concerning medical device vigilance such as medical device reporting and postmarket surveillance. Specifically, SG2 was charged first with reviewing current adverse event reporting, postmarket surveillance and other forms of vigilance for medical devices and performing an analysis of different requirements amongst countries with developed device regulatory systems and then using this information to develop harmonized guidances for data collection and reporting systems. A number of the finalized SG2 guidance documents provide medical device industry standards of practice applicable to the subject matter of this Report, e.g.: (i) Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative;[88] (ii) Manufacturer's Trend Reporting of Adverse Events;[89] and (iii) Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices.[90]

Timothy A. Ulatowski, former Director, Office of Compliance, Center for Devices and Radiological Health (CDRH), U.S. Food and Drug Administration, advised device manufacturers at the 2009 AAMI/FDA Conference on Medical Device Standards and Regulation to keep apprised of the GHTF, as its new standards and guidance documents could influence FDA regulation, stating that "Companies need to become more aware because we're all moving in this direction…GHTF is becoming the global nomenclature."[91]

9. Underreporting of Adverse Events

The FDA relies on the MedWatch postmarketing surveillance program to monitor drug (and biologics) adverse reactions through a database known as the FDA Adverse Event Reporting System (FAERS) and the MAUDE database for Medical Device Reporting. Despite these mandatory and voluntary reporting programs, postmarket adverse event underreporting is pervasive throughout the system. The FDA recognizes that only a small percentage of the total burden of adverse events is captured through MedWatch and "generally assumes that only 1 in 10 adverse (drug) events is reported."[92] Although device-related adverse events are at least as common as drug-related events in the hospital, in-hospital device use and device-related problems are poorly documented.[93, 94] This vast under-recognition of device-related

[88] GHTF FINAL DOCUMENT: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative. June 29, 1999.
[89] GHTF FINAL DOCUMENT: Manufacturer's Trend Reporting of Adverse Events. January 2003.
[90] GHTF FINAL DOCUMENT: Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices. November 30, 2006.
[91] Ulatowski: GHTF to Guide FDA Regulations, Guidances. *The QMN Weekly Bulletin.* April 17, 2009; Vol 1 No 16.
[92] Drazen JM et al. Current adverse event reporting systems. Adverse Drug Event Reporting: The Roles of Consumers and Health-Care Professionals: Workshop Summary, Forum on Drug Discovery, Development, and Translation. *National Academy of Sciences* 2007.
[93] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events.

problems may help to explain why the rate of postmarket adverse event reporting is even bleaker for medical devices, with congressional reports estimating that as few as 1 in 100 medical device reportable events are actually reported.[95] Bright and Shen estimated that, at the national level, 14% of adverse medical device effects were reported to CDRH in 2003. However, since this estimate was based on hospital discharge records, the true rate of underreporting for this population is unknown but certainly less than 14%.[96] Reasons for underreporting of adverse events include, among others, that healthcare providers may be too busy or fail to see that reporting would be useful, may be unaware of the FDA medical device adverse event reporting program, or fear blame for the medical device adverse event.[97]

H. Recalls

FDA defines "recall" as a "firm's removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure."[98] "Removal means the physical removal of a device from its point of use to some other location for repair, modification, adjustment, relabeling, destruction, or inspection."[99] A "correction" is defined as "the repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a device without its physical removal from its point of use to some other location."[100,101]

Recalls may be initiated by a medical device manufacturer, or they may be conducted by the manufacturer at FDA's request or by FDA order under statutory authority.[102] Recalls initiated by the manufacturer or conducted upon FDA's request are considered voluntary recalls. Those conducted in response to FDA order are mandatory recalls. In practice, almost all medical device recalls are voluntary.

A manufacturer's decision to conduct a voluntary recall is based on a determination that the product is violative under the FDCA and that the FDA would be likely to initiate legal action. In making such determination, the manufacturer should consider if a violation of the adulteration and misbranding provisions of the FDCA exists. Under 21 CFR Part 7, a field correction can be done as appropriate if a manufacturer determines a recall is necessary. To continue the marketing and sale of violative product may constitute prohibited acts under the FDCA.

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[94] Samore MH et al. Surveillance of medical device-related hazards and adverse events in hospitalized patients. *JAMA* 2004;291:325-334.
[95] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events.
[96] Bright RA and Shen J. Use of a free, publicly-accessible data source to estimate hospitalizations related to adverse medical device events. Draft manuscript, 2005.
[97] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological Aspects of Postmarket Medical Device Safety.
[98] 21 CFR § 7.3(g).
[99] 21 CFR 806.2(i).
[100] 21 CFR 806.2(d).
[101] 21 CFR § 7.3(h).
[102] FDCA § 518, 21 U.S.C. § 360h.

III. CLINICAL BACKGROUND: STRESS URINARY INCONTINENCE (SUI)

A. SUI Overview

Incontinence occurs when the normal relationship between the lower urinary tract components (bladder, urethra and sphincter, pelvic floor and the nervous system) is disrupted, resulting from nerve damage or direct mechanical trauma to the pelvic organs. Advancing age, higher parity, vaginal delivery, obesity and menopause are associated with an increase in risk. There are different types of urinary incontinence. Stress incontinence (SUI) is the symptom of involuntary loss of urine during situations of increased intra-abdominal pressure, such as coughing or sneezing. Obesity and smoking are also risk factors for SUI.[103] Two types of stress incontinence are recognized, one from a hypermobile but otherwise healthy urethra and one from deficiency of the sphincter itself. Urethral hypermobility is a manifestation of weakened support of the proximal urethra while sphincter deficiency is an indication of compromised ability of the urethra to act as a watertight outlet. There is no standardized test to differentiate between them accurately, and there is increasing belief that both types are present most of the time although to differing degrees. Urge incontinence is the symptom of involuntary loss of urine associated with a sudden, strong desire to void (urgency). It is usually a manifestation of uncontrolled bladder wall contraction (detrusor overactivity). Mixed incontinence is the condition of urine leakage with features of both stress and urgency.

Conservative therapy, with or without the use of medications, is generally undertaken before resorting to surgery. Examples of nonsurgical treatment options for SUI include:

- Pelvic Floor Exercises: A type of exercise to strengthen the pelvic floor by contracting and relaxing the muscles that surround the opening of the urethra, vagina, and rectum. These exercises, commonly referred to as Kegel exercises, improve the muscles' strength and function and may help to hold urine in the bladder longer.
- Pessary: A removable device that is inserted into the vagina against the vaginal wall and urethra to support the bladder neck. This helps reposition the urethra to reduce SUI.
- Transurethral Bulking Agents: Collagen injections around the urethra that make the space around the urethra thicker, thus helping to control urine leakage. The effects may not be permanent.
- Behavioral Modification: This includes avoiding activities that trigger episodes of leaking.

Surgery to decrease or prevent urine leakage can be done through the vagina or abdomen. The urethra or bladder neck is supported with either stitches alone or with tissue surgically removed from other parts of the body such as the abdominal wall or leg (fascial sling), with tissue from another person (donor tissue) or with material such as surgical mesh (mesh sling). Surgical mesh in the form of a "sling" (sometimes called "tape") is permanently implanted to support the urethra or bladder neck in order to correct SUI. This is commonly referred to as a "sling procedure." The use of surgical mesh slings to treat SUI provides a less invasive approach than

[103] Medical Devices: Stress Urinary Incontinence (SUI), http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm

non-mesh repairs, which require a larger incision in the abdominal wall. The multi-incision sling procedure can be performed using three incisions, in two ways: with one vaginal incision and two lower abdominal incisions, called retropubic or TVT; or with one vaginal incision and two groin/thigh incisions, called transobturator (TVT-O). There was also a "mini-sling" procedure that utilized a shorter piece of surgical mesh, which could be done with only one incision.

The number of women who undergo surgery for SUI has increased significantly over the last three decades, both for overall and age-adjusted procedures.[104,105] From January 1979 to December 2004, a cross-sectional study was performed in which data abstracted from the National Hospital Discharge Survey (NHDS) showed that approximately 2,064,940 SUI surgeries were performed in the US.[7] In 1979 (prior to the introduction of the TVT procedure), 48,345 surgeries were performed, compared to 103,467 in 2004. Rates of incontinence surgeries increased by 1.4% per year overall and 4.4% per year in women ≥52 years of age. Retropubic urethral suspension procedures such as the Burch colposuspension decreased over the time period. Suburethral sling procedures increased from 1,591 in 1979 to a peak of 10,212 in 1997, then decreased to 4,314 in 2004. The decreases seen with traditional retropubic and suburethral sling procedures may be due to the increase in use of midurethral sling procedures, which did not have a separate code in the NHDS database and were therefore likely coded as "Other." Another weakness of this study was that outpatient procedures, which are becoming increasingly common, were not captured. In a study using the Nationwide Inpatient Sample and the National Survey of Ambulatory Surgery, the number of women who underwent surgery for SUI during 2006-2007 was calculated.[8]

Success rates for non-sling (i.e., open abdominal retropubic suspension) and TVT are generally considered to be equivalent and are in the order of 68.9% to 88%, although lower rates have also been cited.[106] A recent overview of complications associated with sling procedures was published by Ortega-Castillo and Neri-Ruiz.[107] Intraoperative complications included bladder perforation (rates ranging from 0% [TVT-O only] to 25% in different studies), nerve lesion (rare), and bleeding, including cases of vascular injury (rates ranging from 0.1% to 2.5%) Surgical experience accounts for at least some of the variability in intraoperative complication rates. Immediate post-surgical complications included hematoma, voiding disorders and infection. Hematomas may resolve spontaneously or require intervention such as drainage (minimally invasive) or laparotomy. Voiding disorders (urinary retention, difficulty in voiding) often are short-lived and most can be managed by intermittent catheterization for a period of days. In some cases, the sling may need to be released or cut. Infection may be managed by antibiotic treatment or, in extreme cases, debridement or even colostomy. Some patients may

[104] Oliphant SS, Wang L, Bunker CH, Lowder JL. Trends in stress urinary incontinence inpatient procedures in the United States, 1979-2004. Am J Obstet Gynecol 2009;200:521e1-521-e6.
[105] Wu JM, Kawasaki A, Hundley AF, Dieter AA, Myers ER, Sung VW. Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. Am J Obstet Gynecol 2011;205:230e1-230e5.
[106] Lapitan MCM, Cody JD. Open retropubic colposuspension for urinary incontinence in women (Review). 2012 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.; Ward et al. A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: Two-year follow-up. American Journal of Obstetrics and Gynecology (2004) 190, 324-31; Ward et al., Tension-free vaginal tape versus colposuspension for primary stress incontinence 5-year follow up, *BJOG*, 2008.
[107] Ortega-Castillo V, Neri-Ruiz ES. Surgical complications with synthetic materials, Urinary Incontinence. Alhasso A, ed. InTech, 2012. http://www.intechopen.com/books/urinary-incontinence/complications-of-genital-prolapse-and-urinaryincontinence-surgery

develop a chronic infection causing symptoms years after sling placement. Late complications include de novo urgency, voiding disorders, pain and suprapubic discomfort, mesh erosion/extrusion, intestinal lesion, nerve lesion and dyspareunia.

B. Food and Drug Administration Search of the MAUDE Database

In 2011, FDA convened an Obstetrics & Gynecology Devices Advisory Committee Meeting to discuss the use of surgical mesh for treatment of pelvic organ prolapse (POP) and SUI. As part of their presentation, FDA presented an executive summary that included results of searches of the MAUDE database. Data from the search covering the 2008-2010 timeframe are presented here because FDA presented POP and SUI complications separately. This search identified 2,874 MDRs for urogynecologic surgical mesh, with slightly less than half associated with SUI repairs; notably, these MDRs were additional to the 1,000 that the Agency had identified previously in its 2008 search of the MAUDE database for the years 2005-2007. Adverse events associated with SUI sling procedures included pain, mesh erosion, infection, urinary problems, organ perforation, incontinence recurrence, bleeding, dyspareunia, neuromuscular problems and vaginal scarring. (Please also reference Section IX. for additional information.)

IV. REGULATORY HISTORY: ETHICON'S SURGICAL AND TRANSVAGINAL MESH PRODUCTS

A. Methodology Used and Construction of Regulatory History

To review and evaluate the overall regulatory history of Ethicon's surgical mesh products, a simple search of FDA's searchable 510(k) database was conducted for the following terms:

- Ethicon
- Surgical mesh
- Gynecare
- Product code FTL
- Product code OTN
- TVT
- Johnson & Johnson (J&J)
- Boston Scientific

The J&J simple search was further refined using an "advanced search" for the following parameters:

- J&J, surgical mesh; 1 Jan 1998 to the present
- Ethicon, surgical mesh; 1 Jan 1998 to the present

The result of these searches is presented in Tables IV.1, IV.2, IV.3, and IV.4 and provides a hierarchic representation of the product development and predicate history that eventuated in the marketing of the GYNECARE Tension Free Vaginal Tape (TVT) System. For each mesh product presented, the 510(k)-cleared indications for use, the 510(k) number, the date FDA received the 510(k), the date FDA cleared the device for marketing [510(k)-clearance], and predicate information are provided.

Additionally, I reviewed the 510(k) applications and associated documentation from Ethicon's 510(k) files of particular relevance to the subject matter of this Report and reviewed deposition testimony in which 510(k) submissions and the regulatory process were discussed. Key information pertinent to an understanding of the development and regulatory history of the TVT product is presented in the following section.

B. Overview: Development and Regulatory History of Ethicon's Surgical and Transvaginal Mesh Products

PROLENE nonabsorbable polypropylene suture, the first of Ethicon's surgical mesh product line, was initially regulated as a drug and approved by NDA 16374 prior to the enactment of the Medical Device Amendments (MDA) on May 28, 1976. Following passage of the MDA, devices that had been regulated previously as new drugs and approved under New Drug Applications (NDAs) were officially given device status as "transitional devices." A Premarket Approval application (PMA) number with "N" before the application number (which is the original NDA number) denotes a transitional device; the PMA Number for PROLENE is PMA N16374. (The original approval could not be located through online search efforts that included a search of the FDA PMA database, a general search of CDRH, a search of "drugs @ FDA" for approved drug products, and a "Google" search. However, a listing of the supplements to this PMA was found, with a December 31, 1980, decision date for Supplement 001.)

Reclassification as a polypropylene nonabsorbable surgical suture class II device (21 CFR 878.5010), for use in general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological procedures, was published in the Federal Register on May 31, 1991 (Volume 56, No. 105, Pages 24684-24685). This product is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart E, Surgical Devices, Nonabsorbable Polypropylene Surgical Suture. Also in 1991, PROLENE Polypropylene Mesh Plug W/onlay patch was cleared (510(k) Number K915774) under classification regulation 878.3300: surgical mesh defined as metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples are for hernia repair, acetabular and cement restrictor mesh used during orthopedic surgery. This product also is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart D, Prosthetic Devices, Surgical Mesh. All the remaining products discussed in this review were 510(k)-cleared under the classification regulation 21 CFR 878.3300.

The first of 13 Ethicon 510(k)s that could be identified from the 510(k) searchable database for the repair of hernia defects was submitted to FDA in 1996 and was a modification of the PROLENE Polypropylene nonabsorbable synthetic surgical mesh. According to the 510(k) Summary of Safety and Effectiveness, the modified device has the same technological characteristics as the predicate device (i.e., no change in chemistry, material or composition),

but differs from the predicate device in the additional sizes supplied and a precut key hole shape provided as a convenience to the surgeon.[108]

The first of seven 510(k)s (discussed further below) for GYNECARE Tension-free Vaginal Tape (TVT) System and its various line extension devices was granted 510(k)-clearance in 1998 (510(k) Number K974098). This product, the TVT retropubic device which is the subject of this Report, is a pubourethral sling for the treatment of stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT device is composed of PROLENE polypropylene mesh (tape), and the mesh is covered with a polyethylene sheath with a slit in the middle.[109]

In 2000, PROLENE Soft Polypropylene Mesh, which is knitted by a process which interlinks each fiber junction, allegedly provided for elasticity in both directionsand is claimed to be 50% more flexible than PROLENE, according to the description in the 510(k) Summary of Safety and Effectiveness,[110] was granted 510(k)-clearance (510(k) Number K001122) based on substantial equivalence to Ethicon's PROLENE (Polypropylene) and MERSILENE Meshes (Ethicon polyester mesh). All three of these products, i.e., PROLENE Soft (Polypropylene) Mesh, PROLENE (Polypropylene) Mesh and Mersilene Mesh, served as the predicates for the January 2002 GYNEMESH PROLENE Soft (Polypropylene) Mesh 510(k)-clearance for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect. (Emphasis added.)

Table IV.1 Ethicon Surgical Mesh Regulatory History – Other Indications for Use (i.e., not for hernia, stress urinary incontinence, or pelvic floor repair)

510(k) History: Regulation 878.3300

510k #/ date FDA rcvd/ date cleared	Name	Predicate	Indications for use
K915774 12/24/91 03/02/92	PROLENE Polypropylene Mesh Plug W/onlay patch	Unavailable	Unavailable

[108] FDA 510(k) Searchable Database: K962530 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K962530.pdf.
[109] FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K974098.pdf.
[110] FDA 510(k) Searchable Database: K001122 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K001122.pdf.

510(k) History: Regulation 878.5010

510k #/ date FDA rcvd/ date cleared	Name	Predicate	Indications for use
K001625 5/17/00 7/10/00	Pronova Nonabsorbale suture	Surgilene and PROLENE sutures	In general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological procedures.

Table IV.2 Ethicon Surgical Mesh Regulatory History – 510(k) History: Hernia Repair: Regulation 878.3300

510k # date FDA rcvd/ date cleared	**Name**	**Predicate**	**Indication/intended use**
K962530 6/28/96 8/9/96	Modified PROLENE Polypropylene mesh nonabsorbable synthetic surgical mesh	PROLENE polypropylene mesh nonabsorbable synthetic surgical mesh	Repair of hernia and other fascial deficiencies that require the addition of a reinforcing or bridging material.
K972412 6/26/97 9/10/97	PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant	Bard® Marlex® Mesh Perfix® Plug Nonabsorbable Polyproylene surgical mesh device	Repair of inguinal hernia defects, both indirect and direct.
K984220 11/25/98 2/23/99	Modification: PROLENE(Polypropylene) Hernia System	(Polypropylene) Hernia System	Repair of abdominal wall hernia defects.
K001122 4/7/00 5/23/00	PROLENE Soft (Polypropylene) Mesh	PROLENE (Polypropylene) Mesh and Mersilene Mesh	Repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

Table IV.3 Ethicon Surgical Mesh Regulatory History – 510(k) History: Pelvic Floor Repair: Regulation 878.3300

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication/intended use
K013718 11/8/01 1/8/02	Gynemesh PROLENE Soft (Polypropylene) Mesh	PROLENE Soft (Polypropylene) Mesh, PROLENE (Polypropylene) Mesh, and MERSILENE Mesh	Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect

Table IV.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300

510k # date FDA rcvd/ date cleared	Name	Predicate[a]	Indication(s) or Intended Use
K963226 08/12/1996 11/15/1996	ProteGen Sling Cleared under device name "Surgical Fabrics"	K945377 Trelex Natural Mesh K961810 Supple Peri-Guard K930822 Gore-Tex Soft Tissue Patch Marlex Mesh Mersilene Mesh	Intended to reinforce soft tissue where weakness exists for the urological, gynecological and gastroenterological anatomy inclusive but not limited to the following procedures: pubourethral support, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, and sacro-colposuspension.
K974098 10/30/97 1/28/98	Gynecare TVT Tension-free Vaginal Tape	K963226 ProteGen Sling Collagen Impregnated Material	As a pubourethral sling indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT Introducer and Rigid Catheter Guide accessories are intended to facilitate the placement of the TVT device.

Table IV.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication
K012628 8/13/01 10/26/01	TVT System with three accessories (modification)	K974098 Gynecare Tension Free Vaginal Tape (TVT) System with Accessories: TVT reusable introducer TVT reusable rigid catheter guide Cook OB/GYN Stamey Needle	Same (As a pubourethral sling indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT Introducer and Rigid Catheter Guide accessories are intended to facilitate placement of the TVT device.)
K033568 11/13/03 12/8/03	Gynecare TVT Obturator Device	K974098 and/or K012628 (not specified in available documentation) Gynecare TVT Device	For the treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.
K052401 9/1/05 11/28/05	Gynecare TVT Secur System	K974098 and K012628 Gynecare TVT System K033568 Gynecare TVT Obturator	For the treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.
K100485 2/19/10 3/16/10	Gynecare TVT Exact Continence System	K974098 Gynecare TVT Tension Free Vaginal Tape	As a pubourethral sling for treatment of female Stress Urinary Incontinence, resulting from urethral hypermobility and/or intrinsic sphincter deficiency.

Table IV.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication
K100936 4/5/10 7/1/10	Gynecare TVT Abbrevo Continence System	K033568 Gynecare TVT Obturator System	Same (As a pubourethral sling for treatment of female Stress Urinary Incontinence, resulting from urethral hypermobility and/or intrinsic sphincter deficiency.)
K132054 07/09/2013 08/23/2013	Gynecare TVT Exact Continence System	K100485 Gynecare TVT Exact Continence System	Same (As a pubourethral sling for treatment of female Stress Urinary Incontinence, resulting from urethral hypermobility and/or intrinsic sphincter deficiency.)
[a] Predicate names are reproduced as written in the Summaries of Safety and Effectiveness and may therefore not match exactly between 510(k)s.			

V. REGULATORY HISTORY: GYNECARE TVT™ RETROPUBIC SYSTEM AND LINE EXTENSION FAMILY OF PRODUCTS

A. Methodology Used and Construction of Relevant History

To review the regulatory history specific to the Gynecare TVT Retropubic System (TVT or TVT Classic), the subject of this Report, I principally looked at 510(k) applications, the documentation in Ethicon's 510(k) and related files, and the FDA's searchable 510(k) database. Additionally, I reviewed deposition testimony in which the regulatory process was discussed in some detail. The 510(k) clearance for TVT, including the 510(k)-cleared indications for use, the 510(k) number, the date FDA received the 510(k), and the date FDA cleared the device for marketing (510(k)-clearance) are provided above in Table IV.4. Also shown in Table IV.4 are the line extension products in the TVT family of products.

B. Overview: Regulatory History of Ethicon's TVT Slings for Stress Urinary Incontinence

The first preconfigured sling product cleared for use was the ProteGen Sling in 1996, manufactured by Boston Scientific Corporation (K963226).[111] The ProteGen sling was a woven polyester mesh impregnated with bovine collagen. Among its intended uses was "pubourethral support." Boston Scientific cited five predicates for the ProteGen Sling. Two of the predicates were constructed of polypropylene (Trelex Natural Mesh, Marlex Mesh), one was a polyester mesh (Mersilene Mesh, a pre-amendment device), one was bovine pericardium cross-linked with glutaraldehyde (Supple

[111] FDA 510(k) Releasable Database: K963226 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K963226.pdf

Peri-Guard), and one was polytetrafluoroethylene (Gore-Tex Soft Tissue Patch). Only Supple Peri-Guard has a 510(k) summary available in the FDA's releasable 510(k) database. The Protegen Sling was withdrawn from the market by Boston Scientific in January 1999 due to complaints of mesh complications, including discomfort, dyspareunia, and mesh erosion.[112] The FDA found that the product was "misbranded and adulterated" and did "not appear to function as intended."[113]

Ethicon's first TVT sling was the Gynecare Tension-Free Vaginal Tape System. Ethicon entered into an agreement on February 14, 1997, with Medscand, the company that Pr. U. Ulmsten, a Swedish surgeon who developed the TVT procedure, relied upon to obtain prototypes for clinical use and that had applied for a patent.[114] Ethicon submitted the 510(k) for the TVT System to FDA on October 30, 1997, and received clearance to market on January 28, 1998 (K974098).[115] The ProteGen sling was the predicate device. The Gynecare TVT (Retropubic) System is comprised of a polypropylene (Prolene) mesh tape covered with a polyethylene sheath, a stainless steel TVT Introducer to facilitate passage of the tape from the vagina to the abdominal skin, and a TVT Rigid Catheter Guide that adds rigidity to the Foley catheter during surgery. According to the Summary of Safety and Effectiveness, the Ethicon TVT was the same **technologically** as the predicate; i.e., "**both are meshes that provide pubourethral support**". Further, "**Any differences between the two devices do not raise new questions of safety and effectiveness.**" [Emphasis added.]

In their 510(k) submission, Ethicon presented data from three clinical trials.[116] The first was an abstract containing preliminary data by Wang and Lo (undated). In this study, 70 women were treatedfor SUI according to the Ulmsten procedure. Follow-up was from 3-12 months. Three bladder perforations were reported and 11/70 patients had blood loss > 200mL requiring an indwelling catheter and vaginal tamponade. No defects in healing healing or tape rejection were reported. The second was the 1996 Ulmsten paper that described the original procedure performed by Pr. Ulmsten.The third was an ongoing Scandinavian multicenter study that had preliminary data from 131 patients implanted with the intravaginal slingplasty (IVS) device. Only early postoperative complications were presented. In the Ulmsten study, five patients experienced delayed voiding requiring an indwelling catheter for the first night after surgery, and five patients developed a urinary tract infection that resolved with antibiotic treatment. No instances of tape rejection or defect in healing were reported. In the Scandinavian study, delayed voiding occurred in four patients, three of whom required catheterization from one to three days; the fourth required intervention. There was one case of a bladder perforation, one hematoma, and one case of vaginal infection requiring resection of exposed mesh. .

It should be noted that all of the clinical data support (as set forth above) submitted by Ethicon in support of the 510(k) for the TVT was data from small studies that utilized the IVS device, not the actual TVT device. It is appears from the testimony in this case that the IVS device was different

[112] Nussbaum A, et al. J&J Mesh Approved by FDA Based on Recalled Device. Bloomberg article (2011). http://mobile.bloomberg.com/news/2011-10-20/j-j-vaginal-mesh-approved-by-fda-based-on-older-recalled-device

[113] Cohen R, et al. A surefire profit-maker could cost its maker dearly. The Star-Ledger (2002). http://www.nj.com/specialprojects/index.ssf?/specialprojects/implants/implantsside2.html

[114] ETH.MESH.03932912 at 913-914: The history of TVT by A. Arnaud, MD, July 12, 2000. It should be noted that Pr. Ulmsten was a shareholder of Medscand. ETH.MESH.09748308: Project TOMEL Due Diligence Summary.

[115] FDA 510(k) Releasable Database: K962530 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K962530.pdf

[116] Ethicon Tension-free vaginal tape (TVT) System 510(k) notification. Exhibit No. 415.

from the TVT device in several respects although, admittedly, Ethicon's employees' testimony in this regard is unclear as to exactly what the differences between the devices are. For instance, Laura Angelini, Ethicon's marketing manager in Europe[117] at the time of the launch of the TVT, testified that the mesh used in the TVT was different than the IVS mesh.[118] Axel Arnaud, Ethicon's Medical Director in Europe at the time of the TVT launch, testified that there were differences between the devices including differences in the connection between the mesh and the needles and that the needles were different.[119] Regardless of the differences, the FDA should have been told that the clinical data used to support the TVT submission was developed in studies with different devices.

In addition, Ethicon should have disclosed to the FDA that the studies submitted to support the TVT were performed by investigators (including Pr. Ulmsten) with significant conflicts of interest and, further, that Ethicon paid Medscand $400,000 for the multicenter Scandinavian study only because the study resulted in "favorable results."[120] Professor Ulmsten and Medscand were paid millions by Ethicon, and they were the ones responsible for data from the studies. The FDA should have been told that was the case.

VI. KNOWN HOST RESPONSES AND COMPLICATIONS ASSOCIATED WITH POLYPROPYLENE AND SYNTHETIC MESH

A. Polypropylene (PP) Not Biologically Inert: Inflammatory/ Foreign-Body Responses to PP

Although synthetic materials often are referred to as chemically or physically inert, none is truly biologically inert.[121] Synthetic materials such as polypropylene are known to induce an acute inflammatory response, followed by chronic inflammatory reaction, which elicits a foreign-body response characterized by formation of granulation tissue and fibrosis. The nature of the implant material, including chemical and physical structure, amount of material and surface of the contact area with the patient's tissue, filament and pore size, determines the extent of the inflammatory reaction as well as further tissue in-growth. Other factors, such as material degradation, also may influence inflammatory activity. While the inflammatory phases are necessary for the desired fibrosis process, they may be the source of adverse effects, including implant shrinkage, erosion, and adhesion formation.[122]

Mesh was known to cause an inflammatory response and be subject to shrinkage by the time of TVT launch in 1998. A study in dogs showed that meshes could shrink by 30% (Soft Hernia Mesh multifilament) to 50% (Marlex monofilament) as little as four weeks after implantation.[123] The

[117] Laura Angelini Deposition, September 16, 2013, 18:6-25.
[118] Laura Angelini Deposition, September 16, 2013, 184:4 to 186:10
[119] Axel Arnaud Deposition, July 20, 2013, 521:2-522:20; 462:15-465:17; 503:8-503:19
[120] Laura Angelini Deposition, September 16, 2013, 101:6-110:2; 111:19-112:7; 124:12-15; ETH.MESH.09746948: License and Supply Agreement between Johnson & Johnson International and Medscand Medical A.B.
[121] Deprest J et al. The biology behind fascial defects and the use of implants in pelvic organ prolapse repair. Int Urogynecol J 2006;17:S16-S25.
[122] Deprest J et al. The biology behind fascial defects and the use of implants in pelvic organ prolapse repair. Int Urogynecol J 2006;17:S16-S25.
[123] Klinge U, Klosterhalfen B, Muller M, Ottinger AP, Schumpelick V. Shrinking of polypropylene mesh in vivo: an

amount of mesh contraction correlates with the degree of inflammation and scar formation. Histological analysis showed that both types of meshes induced an inflammatory response, but it was less for the multifilament mesh containing less polypropylene than for the monofilament mesh.[124] The following year, the same group published a study of the inflammatory response to explanted meshes used to repair hernias in humans.[125] Various types of mesh were included in the study (1 polyester, 10 polypropylene, 2 reduced polypropylene, 4 polytetrafluorethylene (PTFE), and 1 absorbable polyglactin). Some of the meshes had been inside the body for years. The partial volume of inflammatory cells varied among the types of meshes tested: polypropylene 32%; PTFE 12%; polyester 8%; and reduced polypropylene 7%. The authors concluded that inflammation induced by the use of alloplastic (synthetic) materials can persist for many years.

The biocompatibility (or bioincompatibility) of synthetic implants is thought to be responsible for various complications of mesh implantation. Three types of mesh materials used for hernia repairs were studied in a rat implantation model: polypropylene (Prolene), polyethylene terephthalate (PET, Mersilene) and polypropylene/polyglactin (PP+PG, Vypro).[126] Histochemical analysis of the inflammatory response was performed at 7 and 90 days after implantation. In all groups, a persisting T-cell response was observed. Colonization of the interface with macrophages showed a pronounced reduction in the PP+PG-mesh group. Infiltration of mast cells at the tissue graft interface showed a time-dependent decrease in the PET- and PP+PG-mesh groups, whereas in contrast, index of mast cells increased in the PP-mesh group. At both time points, indices of proliferation were highest in the PP-mesh group. The authors concluded that these data confirmed the development of biomaterial-dependent chronic inflammatory response to surgical meshes and urged further research on the recruitment of inflammatory cells. Notably, the TVT mesh is "prepared from the same raw material used in the manufacture of PROLENE polypropylene suture."[127] The TVT mesh is PROLENE polypropylene mesh "constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE polypropylene nonabsorbable surgical suture."[128]

A study of explanted polypropylene hernia meshes was performed in an attempt to explain pain and recurrences experienced after hernia repair and the results were published in 2007.[129] The objective of the study was to determine whether oxidation plays a role in the degradation of polypropylene mesh in vivo. After implantation of mesh, the body mounts a prolonged inflammatory response, in which phagocytic cells are continually recruited to the site via a process involving oxygen metabolism and release of superoxide radicals and strong oxidants such as hydrogen peroxide and hypochlorous acid. As a result, the mesh material is exposed to a continuous bath of oxidants. In

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experimental study in dogs. Eur J Surg 1998;164(12):965-969. Abstract only.

[124] Klinge U, Klosterhalfen B, Muller M, Ottinger AP, Schumpelick V. Shrinking of polypropylene mesh in vivo: an experimental study in dogs. Eur J Surg 1998;164(12):965-969. Abstract only.

[125] Klinge U, Klosterhalfen B, Muller M, Schumpelick V. Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J surg 1999;165(7):665-673. Abstract only.

[126] Rosch R, Junge K, Schachtrupp A, Klinge U, Klosterhalfen B, Schumpelick V. Mesh implants in hernia repair. Inflammatory cell response in a rat model. Eur J Surg 2003;35(3):161-166. Abstract only.

[127] 510(k) Number K974098: Biocompatibility Testing Results, page 40.

[128] 510(k) Number K974098, Updated Package Insert, submitted January 21 1998, in response to FDA fax request (no Bates number).

[129] Costello CR, Bachman SL, Ramshaw BJ, Grant SA. Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater Res Part B:Appl Biomater 2007;83B: 44–49.

this study, the authors characterized 14 hernia mesh explants removed from patients due to complications requiring surgery. Samples were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), thermogravimetric analyis (TGA) and compliance testing. SEM showed cracks and fissures in explanted meshes that were not present in control material. DSC also showed changes from control mesh, indicating that oxidation may have occurred; however, not all of the results were statistically significant. TGA (commonly used to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition, oxidation, or loss of volatiles) showed that most of the explanted samples had experienced weight loss in vivo. Compliance testing showed reduced compliance in all but one sample, which is also evidence of oxidation. The authors concluded that oxidation was the most likely cause of in vivo degradation of polypropylene mesh.

A prospective study in 2009 evaluated the inflammatory response to macroporous monofilament polypropylene mesh after surgery for pelvic organ prolapse in 10 patients.[130] Eight patients served as controls (no mesh implanted). Vaginal punch biopsies were performed presurgery and at 1-year post surgery. Foreign body response to the mesh was assessed using a combination of histological, semiquantitative and computerized image-based analysis. Compared to preoperative histology, there was a significant postoperative increase in macrophage and mast cell counts but no significant changes in the count of cells involved primarily in the infectious cell response or collagen density and the elastin fraction at the mesh-tissue interface. Three cases of mild granuloma formation and two cases of mild erosion were observed. There was no significant change in epithelial thickness. The authors concluded that macroporous monofilament mesh induces a mild but persistent foreign body reaction.

The earliest reports that polypropylene could degrade within the human body were published in the 1980s. A review of various plastic materials used in the manufacture of intraocular lenses was published in 1984.[131] The authors concluded that, whereas polypropylene is a highly effective, relatively inert material, there exists evidence that long-term alterations can occur. Two publications in 1986 reported that cracks had developed in polypropylene suture used intracamerally in intraocular surgery.[132,133] In one of these studies, part of the surface layer of the suture was nearly detached or completely missing, and the diameter had decreased by over 50%.

Clave, et al. studied polypropylene and polyester meshes that had been explanted from patients after complications (erosion, infection and/or shrinkage).[134] All explants were either polypropylene or polyester. One hundred (100) explants were studied histologically, by SEM and by chemical analysis. The authors found that polypropylene mesh is altered in vivo, and low density

[130] Elmer C, Blomgren B, Falconer C, Zhang A, Altman D. Histological inflammatory responses to transvaginal polypropylene mesh for pelvic reconstructive surgery. U Urol 2009;181(3):1189-1195. Abstract only.
[131] Apple DJ, Mamalis N, Brady SE, Loftfield K, Kavka-Van Norman D, Olson RJ. Biocompatibility of implant materials: a review and scanning electron microscopic study. J Am Intraocul Implant Soc 1984;10(1):53-66. Abstract only.
[132] Altman AJ, Gorn RA, Craft J, Albert DM. The breakdown of polypropylene in the human eye: is it clinically significant? Ann Ophthalmol 1986;18(5):182-185. Abstract only.
[133] Jongebloed WL, Worst JF. Degradation of polypropylene in the human eye: a SEM study. Doc Ophthalmol 1986;64(1):143-152. Abstract only.
[134] Clave A, Yahi H, Hammou J-C, Montanari S, Gounon P, Clave H. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J 2010;21:261-270.

monofilament mesh was less damaged than nonwoven, nonknitted polypropylene. Polyester mesh suffered the least damage. More degradation was observed in the presence of acute infection or chronic inflammation. The authors concluded that their results question the opinion that polypropylene is an inert substance.

A similar conclusion was reached by Dr. Alex Wang, Chang Gung University Hospital, Taiwan, who hypothesized that polypropylene tape may be rejected after transvaginal implantation via the TVT procedure and proposed a study to investigate the frequency, severity, histological, and immunochemical evidence of rejection.[135,136] Dr. Wang requested funding from Ethicon for this study and although there was some lack of support for Dr. Wang's study proposal at Ethicon,[137] funding ultimately was approved in December 2002.[138] Study results were published two years later, as follows.

Fifteen (15) of 670 TVT patients had sling erosion, defined as defective vaginal healing, for a 2.2% rate of defective vaginal healing post TVT procedure. Conservative treatment, including sitz bath with warm saline solution and local application of neomycin sulfate ointment, was first prescribed for these patients. Those who did not respond to conservative management underwent one or two debridements, i.e., "excision of the inflammatory/granulation tissue and simple closure of the vaginal wound with the suburethral part of the tape embedded."[139] For seven patients, the vaginal wall had not healed four weeks after the second debridement, and the exposed mesh was excised. These wounds healed after mesh explantation, resulting in a persistent defective healing (PDH) incidence of 1%[140] one to seven years after the operation. The authors comment that vaginal erosion may occur after delayed infection of the mesh or prominent foreign body reaction, leading to separation of the vaginal incision and mesh erosion. For the seven women who underwent two debridements and mesh excision, histopathologic findings suggested an immunologic reaction to the polypropylene mesh. Mesh constituents were fragmented and exhibited predominant foreign body reaction, dense fibrosis, and occasional perivascular mononuclear cell infiltration. "The results of this pilot study suggest that polypropylene mesh is not always biologically inert." The authors further noted that "[b]ecause a large and still increasing number of continence taping procedures have been undertaken, there is a clinical and theoretic basis for concern."[141]
Yet Gregory Jones, former Director Regulatory Affairs at Ethicon,[142] testified that if he received this information concerning a pattern of adverse events potentially representing rejection of the TVT mesh in 2002, it would have been of concern to him. However, the IFU for the TVT was

[135] ETH.MESH.00409657: Study Synopsis by Alex C. Wang, MD: Rejection of Polypropylene Tape After the Tension-Free Vaginal Tape (TVT) Procedure.
[136] ETH.MESH.00409670: Email series November 14-December 3, 2002, initiated by Martin Weisberg, RE: Prolene rejection.
[137] ETH.MESH.08793207 at 207-208: Email series October 29-November 11, 2002, initiated by Mark Sumeray, Vice President Clinical Trials, Ethicon Franchise, to Martin Weisberg, RE: Dr. Wang's proposal.
[138] ETH.MESH.00409659 at 660: Customer Initiated Grant Request by Alex C. Wang, MD, approved December 19, 2002.
[139] ETH.MESH.00523348 at 349: Wang AC et al. A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: A prospective case-controlled pilot study. American Journal of Obstetrics and Gynecology 2004;191:1868-74.
[140] ETH.MESH.00523348 at 350: *Id*.
[141] ETH.MESH.00523348 at 353: *Id*.
[142] ETH.MESH.08164608: Gregory Jones resume.

never updated to include this information.[143] Dr. David Robinson testified there is nowhere in the package insert that tells doctors there is a chronic foreign body reaction as a result of the TVT mesh, but, instead, the insert says the foreign body response is transitory.[144]

B. Mesh Shrinkage/Contraction and Associated Morbidities

For all implanted synthetic mesh, there is the issue of inflammatory response and foreign body reaction, as discussed above, particularly as regards the scale, severity, and chronicity of the reaction. The foreign body reaction can lead to scar plate formation resulting in various morbidities, including mesh erosion, pain, and dyspareunia. A chronic rather than an acute inflammatory response/foreign body reaction may result in failure of the device to perform not only safely but effectively.

All of the TVT meshes for stress urinary incontinence are comprised of original, old-construction Prolene mesh 6-mil fiber, with a mass per unit of 100 to 110 grams per meter squared,[145] which is considered heavyweight mesh.[146] A number of companies have developed new mesh systems as a result of increasing numbers of reported mesh-related complications in an effort "to increase efficiency and patient comfort and decrease the side effects and amount of foreign material left in the patient."[147] Ethicon is among those companies and has developed lighter-weight, larger-pore mesh in order to decrease the amount of foreign material left in the body, notably, "[b]ecause the more foreign material that's left in the tissue, the greater the foreign body reaction," which "can create a greater inflammatory reaction" leading to patient complications.[148]

Dr. Holste, whose job at Ethicon is "to evaluate the preclinical safety of a material within the framework of the development,"[149] affirmed that "[o]ne of the problems that a greater inflammatory reaction can cause in the human tissue to a foreign body like a polypropylene mesh implant is that there can be more contraction, sometimes known as mesh shrinkage."[150] "The formation of scar tissue throughout the mesh causes a contraction within the tissue. Since the mesh is compressible along its length it can be acted on by the tissue." This is the cause for shrinkage, not that the mesh itself shrinks.[151] "…[S]hrinkage rate is influenced by many parameters as the degree of fibrotic reaction is dependent on the mesh material/weave/width etc."[152] It appears, based on internal documents, that the "rule of thumb" regarding the amount of shrinkage occurring with the TVT mesh was 30%. [153]

Dr. Holste acknowledged, based on almost 30 years of working at Ethicon on tissue reaction to meshes, that greater inflammatory reaction can entrap nerves, leading to pain, and can cause

[143] Gregory Jones deposition, August 20, 2013, 117:13-118:13.
[144] Dr. David Robinson deposition (rough transcript), September 11, 2013, 280:5-11.
[145] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 38:21-39:6.
[146] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 40:12-15.
[147] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 51:3-12.
[148] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 51:25-52:22.
[149] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 144:20-23.
[150] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 52:23-53:6.
[151] ETH.MESH.03910418 at 420: Email series November 22-26, 2002, RE: Mini TVT – mesh adjustment.
[152] ETH.MESH.03910418: *Id.*
[153] *Id.*

erosions.[154] A heavier-weight mesh like the TVT Prolene mesh results in a greater foreign body reaction and, thus, "will cause a greater inflammatory reaction than a lighter-weight mesh,"[155] which can cause an increased risk of tissue contraction as compared to lighter-weight meshes,[156] during maturation of the collagenous tissue.[157]

The border for scar plate formation in small-pore, standard-weight meshes like the TVT mesh is around 1,000 microns (i.e., one millimeter). Because the pores of TVT mesh are less than one millimeter, the TVT mesh is susceptible to fibrotic bridging and scar plate formation.[158] Dr. Holste agreed that a lightweight, large-pore mesh would have less of an inflammatory response in the tissues around the urethra and there should be concern that heavyweight, small-pore meshes could result in "shrinkage and contraction problems in the tissues underlying the urethra for slings."[159,160] "Yet Ethicon never studied the difference between a lightweight, large-pore mesh in the tissue in and around the urethra for slings versus its old-construction, very first Prolene surgical mesh."[161]

C. TVT Mesh Fraying, Particle Loss, Roping and Deformation and Associated Morbidities

As discussed above in Section V.B., in October 2001 a modification to the TVT System was 510(k)-cleared that provided for the use of blue-pigmented Prolene polypropylene mesh. "[T]he mesh color was changed from clear to blue to assist in seeing the final mesh placement better."[162] "The reason for going to blue was so that the surgeon could see it under the urethra."[163] However, Ethicon documentation reveals that "[f]raying is inherent in the product based on the mesh construction. When any amount of tension is applied to the mesh, fraying occurs. Stretching of the mesh increases the probability of fraying and so apparition of mesh particles."[164] Dan Smith, currently an engineering fellow (June 2013) and an Ethicon employee for 36 years,[165] acknowledged that the mesh fraying "was known to us. It was known to our competitors."[166] "This is not new, and was exactly the original issue that stopped TVT blue for months."[167] The blue color made the particle loss apparent.

A marketing communication from the Director Marketing Europe, Steve Bell, advised that "[a]s more and more customers now move to TVT Blue…you may sometimes hear. 'I can see small blue

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[154] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 55:22-56:13.
[155] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 56:15-21.
[156] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 56:23-57:4.
[157] Joerg Holste, DVM, PhD, deposition, July 30, 2013, 588:23-589:11.
[158] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 62:21-63:1; 78:9-15; 80:7-81:4.
[159] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 116:10-18.
[160] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 156:7-20.
[161] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 156:22-157:4.
[162] ETH.MESH.00858252: MEMO from Allison London Brown to Dan Smith RE: Mechanical Cut vs. Laser Cut Mesh Rationale (undated).
[163] Daniel Smith deposition, June 5, 2013, 177:18-21.
[164] ETH.MESH.03535750: Letter to Mr. Herve Fournier, Ethicon France, from Carol Holloway, Product Complaint Analyst, Worldwide Customer Quality, RE: 810041B TVT Device, Blue Mesh, Reference #6167, our file #30005383, October 12, 2005.
[165] Daniel Smith deposition, June 5, 2013, 28:18-23.
[166] Daniel Smith deposition, June 5, 2013, 160:3-10.
[167] ETH.MESH.00863391: Email series February 27, 2004, From Bernhard Fischer to Janice Burns to Dan Smith, latter's reply, RE: Important: 2 TVT Complaints concerning allegedly brittle mesh.

pieces come off the mesh! What's wrong.'"[168] In regards to this marketing communication, Dan Smith noted in correspondence with Medical Director Charlotte Owens concerning logging complaints that some customers had raised questions "about the blue particles again (the same as when it was released in the states)."[169] This marketing communication made several key points, among which was the following: "The **same** number of particles came off the clear mesh when it was stretched – It's just that you see them against the tissues and skin more when they are blue. – *This is no different to what has happened for the past 7 years with TVT."*[170] Significantly, I found no evidence that mesh fraying with particle loss was noted in the TVT labeling or anywhere in either of the TVT 510(k)s: K974098 and K012628. To the contrary, both 510(k)s state that "[t]he material is not…subject to degradation…"[171]

Thus, it is particularly noteworthy that a few months prior to the submission of 510(k) Number K012628, in response to a complaint about "uneven/inconsistent tape width as well as fraying edges," from Dr. Alex Wang in Taiwan, "one of the most experienced TVT users in the world," Medical Director Dr. Martin Weisberg remarked, "…I don't think we have any idea whether the tape inconsistencies are clinically significant or not, however the appearance of the tape in the appended pictures certainly gives the impression of inconsistent manufacturing and/or quality control."[172] Richard Isenberg further commented, "I agree with Marty. Consistency in manufacturing appears to be at issue. I cannot judge clinical significance from the information available to me…"[173]

The referenced marketing communication further recommended to "[r]eassure your doctors that this is part of the success of TVT. The way we have cut the mesh makes the edges softer and we feel that this has been a crucial success factor in TVT. Reassure them that PROLENE is proven to be inert and there are hundreds of papers going back 25 years to reinforce this point. These particles will not cause any problem."[174] Notably, as discussed above, polypropylene is not biologically inert. When Dan Smith was asked, "So using inert in a technical sense, this is false, isn't it?," he replied, "I probably would have used a different word." Yet it appears "this is what Steve Bell was telling the salespeople to go out and tell doctors."[175]

I reviewed no evidence of any studies conducted to determine long-term whether the fraying and the particles lost inside the body might cause deleterious effects. Instead, as discussed in Section X.D.2., there were complaints related to mesh fraying and particle loss that should have been submitted to FDA as MDR reports in my professional opinion but were not; nor did I review any evidence of follow up of these complaints to determine if there were any long-term sequelae or impact of mesh fraying on TVT effectiveness. Concerns of physicians regarding the mesh fraying are highlighted by a communication from Dr. J. Eberhard, considered an opinion leader in

[168] ETH.MESH.00865322 at323: Email series March 2, 2004, between Dan Smith and Charlotte Owens, RE: Reminder on BLUE mesh!
[169] ETH.MESH.00865322: *Id*.
[170] ETH.MESH.00865322 at323: *Id*.
[171] ETH.MESH.08476210 at 224: 510(k) Number K974098; ETH.MESH.00748310 at 341: 510(k) Number K012628.
[172] ETH.MESH.03905472 at 473-474: Email series April 23-June 6, 2001, initiated by Richard Hu, Johnson & Johnson Medical Taiwan, RE: TVT recommendation from Dr. Alex Wang.
[173] ETH.MESH.03905472: *Id*.
[174] ETH.MESH.00865322 at 323: *Id*.
[175] Daniel Smith deposition, June 5, 2013, 181:4-11.

Switzerland.[176] Dr. Eberhard returned a TVT tape used for demonstration for patients before their surgery, remarking as follows:

> "Already at the operation it is embarrassing to see how the tape is crumbling. But it gets worse if there is a stretch on the tape.
>
> It is urgent that Johnson & Johnson quickly produce a tap [sic] that is solid and weaved. If not I have the convenience that the doctors will change the taps [sic] and will get others (from other suppliers).
>
> I can't understand, that no one will solve that problem for such a long time. At the latest, as the tap [sic] has becoming blue, everyone has realized that the quality of the tape is terrible…"[177]

In August of 2006, Gene Kammerer, an Ethicon Engineering Fellow, described in a powerpoint including photos how the TVT mechanically cut mesh responded when stretched 50%. He describes and the photos depict significant degradation, loss of structure, fraying, roping and deformation that occurs to the mechanically cut mesh as opposed to the laser cut mesh (LCM).[178] Roping of the TVT mesh was known to Ethicon and was a source of frequent complaints from physicians.[179] In fact, some at Ethicon felt that TVT was losing business daily because of the mesh elasticity and roping.[180]Peer reviewed literature supports that the TVT easily becomes permanently deformed with very little tension when compared to other polypropylene slings.[181]

Thus it was, effective fourth quarter 2006, that Ethicon moved from mechanical cut mesh (MCM) to also making LCM available.[182] It was announced that this change was made to gain efficiencies in manufacturing processes but the announcement also noted that it was found that laser cutting "reduced particulate loss as well as the potential for mesh fraying."[183] The announcement of the availability of LCM (dated as approved on June 26, 2006) advised that "[t]he laser cut mesh will be available for you to sell as needed, particularly to customers that have voiced concerns regarding particle loss and fraying."[184] Notably, the Clinical Expert Report signed by both Dr. Martin Weisberg and Dr. David Robinson[185] in regards to the laser cut mesh notes that "the need for

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[176] ETH.MESH.02180826-827: Email series November 12, 2004, between David Menneret, Complaint investigator/Regulatory contact, and Sibylle Basso, RE: Dr EBERHARD letter.
[177] ETH.MESH.02180833: Translation of PD Doctor Eberhard's letter of 18.10.04.
[178] ETH.MESH 03334244; ETH.MESH.06001408: LCM Project Photographs Comparing Laser Cut Mesh vs Mechanical Cut Mesh; ETH.MESH.00584527: Second half of photo presentation Re: Degradation
[179] ETH.MESH 00526473: Email from Allison London Brown states the Ethicon gets a high number of complaints of the material stretching "to the point of being a string."
[180] ETH.MESH.00440005: Emails Re: Important Laser cut mesh update.
[181] Moalli et al., Tensile properties of five commonly used mid-urethral slings relative to the TVT, *Int. Urogynecol*, 2007.
[182] ETH.MESH.00167119: Product Pointer – GYNECARE TVT Tension-free Support for Incontinence, Approved June 26, 2006, by Marketing Services.
[183] *Id.*
[184] *Id.*
[185] ETH.MESH.00167104: Clinical Expert Report – Laser Cut Mesh for GYNECARE TVT Tension-free Support for Incontinence, GYNECARE TVT Tension-free Support for Incontinence with Abdominal Guides, and GYNECARE TVT Obturator System Tension-free Support for Incontinence, April 18, 2006.

switching from mechanically cut to laser cut mesh arose as a response to customer needs. Customers expressed a desire for a TVT mesh with smoother edges rather than edges with the ends of individual fibers exposed. Customer feedback also indicated that there was some dissatisfaction with the potential fraying effect of mechanically cut mesh."[186] The announcement of availability of the laser cut mesh noted that "the edges of the mesh will appear and may feel slightly different upon stretching," stating that several bench tests were conducted and "the physical properties of both the mechanically cut and laser cut meshes are similar within the range of physiologic forces."[187]

Design verification "shows that sample sets were not statistically different, however the avg% particle loss of MCM is higher than LCM."[188] Testing showed that "[o]n average, the Mechanically Cut mesh lost approximately twice the number of particles as the Laser Cut mesh."[189] Notably, using "the test method from the new French standards for particle loss, the difference between TVT and the competitors is significant. Approximately 10 fold more for TVT at 8% of the strip falling off."[190]

"Qualitative one-on-ones on the topic of Laser Cut Mesh vs. traditionally cut mesh were completed the weekend of Dec 10-11 (year not specified) with several preceptors: Dr. Vince Lucente, Dr. David Robinson, Dr. Dennis Miller, Dr. Jim Raders, Dr. Bob Rogers, Dr. Jaime Sepulveda, Dr. Chip Hanes and Dr. Aaron Kirkemo."[191] With regard to "denaturing/linting," four of these doctors had experienced "previous personal issues with the linting factor. But all expressed concern with it on behalf of other colleagues who may have experienced negative problems with it. Dr. Rogers made note that some peers may replace the first mesh if the linting occurs, as they are concerned with leaving particles in their patient. Dr. Sepulveda said that he had noticed the linting in patients after their next-day adjustment."[192]

The evidence is clear that Ethicon knew early on that the TVT mesh had many characteristics that could lead to adverse outcomes for patients, including that the mesh had frayed edges, lost particles, could deconstruct, deform and rope. In fact, Ethicon's Design Failure Mode Effects Analysis (dFMEA) completed in preparation for launch of the LCM, identified "roping" or "deconstruction" of the mesh as causes of erosion and, further, identified the roughness of the edges of mesh as a cause of pain.[193] Reduction in pore size is also listed as a potential cause of

[186] ETH.MESH.00167104 at 107: *Id.*
[187] ETH.MESH.00167119: Product Pointer – GYNECARE TVT Tension-free Support for Incontinence, Approved June 26, 2006, by Marketing Services.
[188] ETH.MESH.00585842: Email series RE: TVT LCM – particle loss (reimbursement submission), from Sungyoon Rha, response from Gene Kammerer.
[189] ETH.MESH.00167104 at 108: Clinical Expert Report – Laser Cut Mesh for GYNECARE TVT Tension-free Support for Incontinence, GYNECARE TVT Tension-free Support for Incontinence with Abdominal Guides, and GYNECARE TVT Obturator System Tension-free Support for Incontinence, April 18, 2006; BE-2005-1920 Protocol to Evaluate Elongation, Particle Loss and Flexural Rigidity of TVT U PROLENE Mesh Laser-Cut vs. Mechanical-Cut.
[190] ETH.MESH.00585842: Email series RE: TVT LCM – particle loss (reimbursement submission), from Sungyoon Rha, response from Gene Kammerer.
[191] ETH.MESH.01809082: Memo: VOC on new Laser Cut TVT Mesh (undated).
[192] ETH.MESH.01809082 at 83: *Id.*
[193] ETH.MESH 01218019; Dan Lamont testified that the fraying of the mesh is a defect (Dan Lamont deposition,, Sept.11, 2013.

erosion and it was known by the company that reduced pore size can lead to erosions.[194] Despite Ethicon's knowledge of these problems with the mesh, Ethicon decided to continue marketing the TVT mechanically cut mesh even after the LCM mesh was launched and never informed physicians or patients about these risks from the mesh characteristics in its labeling.

D. Biocompatibility Testing and Cytotoxicity

For the TVT System initial 510(k) (K974098), Ethicon determined that "[t]he long clinical experience with PROLENE mesh indicated the cytotoxicity testing would be sufficient to support biocompatibility of this component."[195] Cytotoxicity testing was conducted in accordance with ISO 10993-5 guidelines: "Biological Evaluation of Medical Devices – Tests for Cytotoxicity: In Vitro Methods."[196] The polypropylene mesh component of the sterile TVT device was noncytotoxic in the ISO Agarose Diffusion test but showed moderate to severe cytotoxicity in the ISO Elution test, suggesting cytotoxic potential in this sensitive test system. Of note, previous ISO Agarose Diffusion and ISO Elution cytotoxicity testing of normal production sterile PROLENE mesh indicated this material was noncytotoxic. Nonsterile raw material polypropylene mesh used in the manufacture of the TVT device was also noncytotoxic in the ISO Elution test.[197] Based on my review of the TVT 510(k), Ethicon failed to report to FDA the corroborating results of marked cytotoxicity of the TVT mesh which were observed by Ethicon Scotland in both the ISO Elution test and the ISO Agar Overlay test of the sterile Ulmsten device.[198] Ethicon concluded that "the long history of safe clinical use of [polypropylene] as mesh and suture products suggests strongly that this material is inherently biocompatible, and that the potential cytotoxicity observed is self-limiting and minimal when compared to the implantation procedure itself."[199] It is noteworthy that Ethicon also evaluated the cytotoxicity of competitor products, specifically, the Bard mesh and Surgilene suture, and those products were found to be non-cytotoxic.[200]

Additionally, Ethicon reported to FDA that "[p]olypropylene mesh has been used extensively in humans for many years without clinical evidence of rejection and has proven to be one of the most inert materials implanted in humans." Further, "the healing that occurs over exposed mesh provides strong clinical evidence that this material does not impair wound healing and is not cytotoxic in humans. Implantation of a potentially cytotoxic material would be expected to cause impaired wound healing resulting in non-healing ulcerations and overt evidence of foreign body reaction. Thus, this clinical data provides significant evidence that the potential cytotoxicity of the polypropylene mesh observed in-vitro does not translate into any clinical significance or adverse patient outcomes."[201] Thus, it is important to note that impaired wound healing/wound dehiscence was reported in 3.8% of the TVT MDR reports reviewed on the MAUDE database from 1999

[194] Joerg Holste deposition July 29, 2012, 51:25-56:13; David Robinson deposition September 11, 2013, 1066:8-1070:22.
[195] 510(k) Number K974098: Biocompatibility Testing Results, page 40.
[196] *Id.*, page 41.
[197] 510(k) Number K974098: Biocompatibility Testing Results, page 41.
[198] ETH.MESH.06852118 at 121: Review of Biocompatibility Data on the Tension Free Vaginal Tape (TVT) System for Compliance to FDA G-95/ISO 10993/EN 30993, May 26, 2000, from Richard W. Hutchinson, DVM, PhD, Senior Scientist, Preclinical Safety Assessment, to P. Cecchini.
[199] *Id.*
[200] Dr. David Robinson deposition (rough transcript), September 11, 2013, 288:22-289:8.
[201] *Id.*, page 42.

through 2010. Moreover, mesh erosion and exposure are frequently reported complications of polypropylene mesh, including the TVT device, and were reported in 32.1% of TVT MDR reports reviewed on the MAUDE database from 1999 through 2010. Additionally, as discussed above, Wang et al.,[202] reported a 2.2% rate of defective vaginal healing post TVT procedure in a series of 670 patients implanted with the TVT device and a persistent defective healing rate of 1%. This clinical evidence contradicts Ethicon's statement to FDA that the observed cytotoxicity does not have clinical significance or adverse patient outcomes.

It is remarkable that Dr. David Robinson testified that he never knew during the time he was "the Worldwide Medical Director at Ethicon that there was positive cytotoxicity of the polypropylene mesh used in the TVT product."[203] Notwithstanding the positive cytotoxicity results and the clinical evidence of precisely the types of adverse events Ethicon advised FDA it would expect from cytotoxic material, Dr. Robinson testified he was not aware of any long-term study undertaken by Ethicon to determine whether or not the TVT mesh is clinically cytotoxic in women.[204]

E. Potential for Carcinogenicity as a Result of Chronic Inflammation

Chronic inflammation may predispose to cancer and there are a number of examples of inflammatory conditions associated with cancer in humans, including *H. pylori* and gastric cancer, asbestos and mesothelioma, and hepatitis virus B or C and hepatocellular carcinoma.[205] This may occur via the action of proinflammatory cytokines on cells that have already sustained genetic damage (initiation) but are not yet malignant. Inflammatory cytokines are known to have tumor promoting activity. It is not known whether inflammatory cytokines can cause an initiating event.

Infection is a documented complication of mesh implants, including SUI slings.[206] Implantation may also potentiate an existing infection. Since the body mounts an inflammatory response to infection, chronic or sub-chronic infections may result in long-term inflammation. There is a lack of long-term data in the literature about chronic infection/inflammation after mesh implantation. Most infections are acute, early postoperative complications. However, Dr. Holste testified that it is known that biofilms can attach to meshes, resulting in development of chronic infections and, thus, chronic inflammation which can cause future complications.[207] [Note that a biofilm is "an assembly of bacterial colonies fixed upon a support and locked up into an encapsulating matrix" and resistant to stress and antimicrobials. "Progressively, with (sic) any clear signs of inflammation or infection, the prosthesis will loosen. The microorganisms involved in most cases are common, Staph. A and Staph. E."[208]]

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[202] ETH.MESH.00523348 at 349-350: Wang AC et al. A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: A prospective case-controlled pilot study. American Journal of Obstetrics and Gynecology 2004;191:1868-74.
[203] Dr, David Robinson deposition (rough transcript), September 11, 2013, 286:3-9.
[204] Dr. David Robinson deposition (rough transcript), September 11, 2013, 293:5-11.
[205] Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 2005;7:211-217.
[206] FDA Executive Summary. Surgical mesh for treatment of women with pelvic organ prolapse and stress urinary incontinence. Obstetrics & Gynecology Devices Advisory Committee Meeting September 8-9, 2011.
[207] Joerg Holste, DVM, PhD, deposition, July 30, 2013, 298:7-14.
[208] Joerg Holste, DVM, PhD, deposition, July 30, 2013, 296:24-297:22.

There are two case studies in the literature in which tumors developed in patients with mesh implants. These are discussed below.

The first case study describes a female patient who presented with gross hematuria, urinary urgency and frequency and dysuria 10 weeks after placement of TVT (Gynecare) for urodynamically confirmed SUI.[209] Comparison CTs confirmed that the mass was not present during TVT placement. She was eventually diagnosed with an inflammatory myofibroblastic tumor (IMT) and underwent a transurethral resection with complete resolution of symptoms and no recurrence two years later. IMTs are typically characterized by a mix of inflammatory cells, e.g., plasma cells, lymphocytes and eosinophils, and bland spindle cells without nuclear atypia. The patient's tumor was composed of fascicles of spindle cells with areas of variable cellularity and prominent myxoid change, consistent with IMT. Although rare, postoperative IMTs have been known to follow manipulation of the bladder by biopsy, injury or resection. Postoperative IMTs have also been shown to follow prostate biopsy or resection. This is the first report of such an occurrence after TVT placement. Whereas the patient did not have a visible bladder injury at the time of mesh placement, it is possible that the muscularis layer may have been inadvertently breached without actual perforation. This patient also had a history of neurofibromatosis, but the authors state that no information in the literature suggested a relationship between that condition and the IMT.

The second study describes two male patients who developed squamous cell carcinoma (SCC) years after having mesh hernia repairs.[210] In each case, the SCC was associated with an underlying long-term infection due to the mesh. The first patient had a 24-year history of mesh infection (type of mesh and date of implant not reported). In 1988, he underwent multiple laparotomies due to biliary pancreatitis, leaving exposed mesh. From 2003 to 2007 he underwent several interventions to remove exposed pieces of the mesh, after the last of which he developed an intermittent enteric fistula. In 2012 he was diagnosed with SCC and fluid from his abdominal wall was positive for methicillin-resistant *Staphylococcus aureus*. Resection of the tumor included two segments of the small bowel, part of the transverse colon and removal of the infected mesh. He received adjuvant chemotherapy and his preliminary outcome six months after surgery was good. The second patient had a 6-year history of mesh infection. Following laparotomy for a closed abdominal trauma, he developed an incisional hernia that was treated with polyester mesh reinforcement. One year later the mesh became infected and was partially exposed. Five years after this, he presented with an ulcerated lesion of the skin around the exposed mesh, which was diagnosed as SCC. He underwent resection of the tumor and reconstruction of the abdominal wall, but had a recurrence six months later. Further interventions were unsuccessful and the patient died due to progressive SCC after four months. In both cases, it was felt that the SCC arose in response to long-term infection of exposed mesh, not directly because of the mesh itself.

Although mesh has not yet been implicated as a carcinogen in humans, the known complication of chronic infection as a result of mesh implantation may give rise to other cases of malignancy as a secondary outcome. Polypropylene implants can give rise to local sarcomas in rats,[211] and while

[209] Kwon SY, Latchamsetty KC, Benson J, Carreno M. Inflammatory myofibroblastic tumor of the urinary tract following a TVT. Female Pelvic Med Reconstruct Surg 2012;18:249-251.
[210] Birolini C, Minossi JG, Lima CF, Utiyama EM, Rassian S. Mesh cancer: long-term mesh wall infection leading to squamous-cell carcinoma of the abdominal wall. Hernia, published online 19 April 2013.
[211] Sunoco Material Safety Data Sheet for C4001 Polypropylene. November 20, 2006.

this may not be predictive of human outcomes, there is sufficient evidence of a potential signal to support that manufacturers should perform preclinical carcinogenicity testing of implanted polymers prior to marketing a device. Regardless, the fact that the polypropylene contained in the TVT caused sarcomas in rats should have been disclosed to physicians and patients.

OPINION #1: Failure to Conduct Appropriate Testing

The above information and discussions concerning the potential for persistent foreign body reaction and chronic inflammation, mesh degradation, cytotoxicity, chronic infection leading to chronic inflammation, loss of pore size of the mesh, and the potential for carcinogenicity highlight numerous potential concerns of TVT mesh implantation about which Ethicon not only failed to warn healthcare practitioners and patients but also failed to investigate through appropriate testing. The initiation of the World Registry study was a positive step but, as discussed above, this study was discontinued with no long-term data to address these outstanding concerns potentially impacting not only patient safety but also product effectiveness.

Regarding cytotoxicity, it is notable that Ethicon selected the best data for disclosure to FDA and, thus, did not submit study data that showed marked cytotoxicity in both types of cytotoxicity studies conducted (ISO Elution test and ISO Agar Overlay test conducted by Ethicon Scotland). I reviewed no evidence that Ethicon performed additional testing to elucidate the reasons for the cytotoxicity of the sterile TVT mesh as compared to the non-cytotoxicity of normal production sterile PROLENE mesh and nonsterile raw material polyprolylene mesh. [212]

With regard to mesh fraying and particle loss, I have not seen any evidence of any studies conducted to determine long-term whether the fraying and the particles lost inside the body might cause deleterious effects.

In these multiple ways in my professional opinion, Ethicon failed to perform testing that was critical to learning the long-term safety of the TVT permanent implant. Ethicon fell below the standard of care required of a reasonably prudent medical device manufacturer. Moreover, Ethicon failed to comply with its own credo, specifically, that the company's first responsibility is to the doctors and patients who use Ethicon's products."[213]

VII. TVT CLASSIC: KNOWN/KNOWABLE RISKS

A. Known Potential Complications: Synthetic Mesh in SUI Repair

1. Source: Ethicon Internal Documents and Deposition Testimony

Testimony of Ethicon senior management in both Medical Affairs and Regulatory Affairs confirms that all the risks of the TVT System known today were also known at the time of TVT launch.[214,215]

[212] Thomas Barbolt deposition August 14, 2013 86:4-14; 319:19-21
[213] Exhibit T-115 (no Bates number): Johnson & Johnson credo.
[214] Catherine Beath, July 12, 2013, 608:13-20.

For example, Dr. Piet Hinoul, currently Medical Director worldwide for the Ethicon energy franchise,[216] testified that Ethicon knew all of the potential complications listed below at the time of the TVT launch. This list includes all of the complications associated with transvaginal placement of surgical mesh that were identified in FDA's 2008 *Public Health Notification*. (Please reference Section IX.A.) Both Catherine Beath, Vice President of Quality Assurance and Regulatory Affairs, and Dr. Hinoul testified that Ethicon knew about all of the following complications identified in the 2008 *PHN* at the time of product launch.[217,218]

Dr. Hinoul agreed that all of these complications should be reflected in the TVT labeling; indeed he said "they will be reflected"[219] or "are included in the labeling."[220] Dr. Arnaud agreed it was very important for the company to communicate the known risks of the company to physicians so they would know what they are and to make sure the risks are communicated to patients.[221]

As discussed in Section VIII.A., a number of these complications are not in the TVT labeling, contrary to Dr. Hinoul's testimony.

E. Mesh erosion, e.g., through the vaginal epithelium (with potential for significant pain)
F. Infection
G. Pain
H. Urinary problems
I. Recurrence of incontinence
J. Bowel perforation
K. Bladder perforation
L. Blood vessel perforation
M. Vaginal scarring
N. Dyspareunia[222]

Dr. Hinoul "absolutely" agreed that Ethicon knew at the time of TVT launch that some patients could have complications or failures that would require additional surgery(ies)[223] or other treatments, including intravenous (IV) therapy, blood transfusions, or drainage of hematomas or abscesses.[224] Further, he and Dr. Arnaud acknowledged that Ethicon anticipated the possibility from the time of the TVT launch that a patient might have a TVT implanted and subsequently experience pain, erosion, or other complications that would necessitate removal of the TVT mesh.[225]

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[215] Dr. Piet Hinoul deposition, June 27, 2013, 551:12-552:9.; Dr. Axel Arnaud deposition, July 19, 2013, 125:15-127:1.
[216] Dr. Piet Hinoul deposition, June 26, 2013, 12:24-13:5.
[217] Catherine Beath, July 11, 2013, 233:25-234:8; 245:21-246:1.
[218] Dr. Piet Hinoul deposition, June 27, 2013, 551:12-552:9.
[219] *Id.*, 556:25-557:7.
[220] *Id.*, 557:23-558:4.
[221] Dr. Axel Arnaud deposition, July 19, 2013, 19:25 -21:1.
[222] Dr. Piet Hinoul deposition, June 27, 2013, 547:5-552:9 (testimony inclusive of all complications listed through dyspareunia).
[223] *Id.*, 552:14-21.
[224] *Id.*, 556:3-12.
[225] *Id.*, 554:14-555:11; See also Deposition of Dr. Axel Arnaud for list of known complications including pain, dyspareunia, wound healing difficulties, voiding difficulties, contraction. Deposition of Dr. Axel Arnaud, July 19, 2013, 115:9-127:1.

Ethicon internal documents[226,227] and related testimony[228] provide evidence that Ethicon knew not only about the above-listed potential complications of TVT implantation but also the additional complications listed below "at the time of the launch of the TVT Classic"[229] and, thus, prior to implementation of the first in-use version of the IFU available for review (i.e., in use September 8, 2000).

- Inflammation at the surgical site[230]
- Urinary tract infection (UTI)[231]
- Abnormal postoperative bleeding,[232] including hematoma[233]
- Dysuria[234]
- Hematuria[235]
- De novo detrusor instability or urgency[236]
- Irritation at the wound site[237]
- Fistula formation[238]
- Urethral obstruction due to over-correction with resultant urinary retention[239]
- Venous thrombosis[240]
- Abscess formation[241]

Dr. Hinoul acknowledged that mesh exposure and mesh erosion can be caused by a foreign body response, although he does not consider the foreign body response itself a complication.[242] It is important to note that the risk of erosion of the TVT mesh is a lifelong risk.[243] As Dr. Hinoul pointed out, the device is a foreign body and doesn't resorb, so the mesh can erode into the vaginal wall (termed "exposure") or into the urethra[244] or bladder.[245] Erosions can also be recurrent.[246]

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[226] ETH.MESH.03905059 at 069: Draft Clinical Expert Report GYNECARE TVT SECUR System, August 23, 2005, Section 8: Potential Complications.
[227] ETH.MESH.00658177 at 189-191: Surgeon's Resource Monograph – Expert opinions on the use of GYNECARE TVT Tension-Free Support for Incontinence, A REPORT of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases.
[228] Dr. Piet Hinoul deposition, June 27, 2013, 559:20-560:19.
[229] *Id.*, 575:3-16.
[230] *Id.*, 562:1-3.
[231] *Id.*, 562:16-19.
[232] *Id.*, 562:20-22.
[233] *Id.*, 566:25-567:23.
[234] *Id.*, 562:23-24.
[235] *Id.*, 563:7-9.
[236] *Id.*, 564:10-13.
[237] *Id.*, 565:9-12.
[238] Dr. Piet Hinoul deposition, June 27, 2013, 566:11-14.
[239] *Id.*, 566:15-19.
[240] *Id.*, 567:24-568:4.
[241] *Id.*, 568:13-15.
[242] *Id.*, 566:1-9.
[243] In addition, Ethicon's own long term study comparing TVT to Burch colposuspension concluded that "tape erosion may occur many years after surgery." Ward et al., Tension-free vaginal tape versus colposuspension for primary stress incontinence 5-year follow up, *BJOG*, 2007.
[244] Dr. Piet Hinoul deposition, June 27, 2013, 582:3-9.
[245] *Id.*, 576:18-577:1.
[246] *Id.*, 577:7-15.

Ethicon's former Medical Director also agreed that narrowing of the vaginal wall, while the anticipated risk was very low, could occur and was a known risk at the time of the TVT launch.[247] As noted by Dr. Hinoul, mesh contracture resulting from contraction of the scar around the mesh was a risk Ethicon considered at the time of the TVT launch.[248] He conceded that in rare instances such contracture "can cause pain and significant discomfort for the patient."[249] Moreover, he acknowledged that pain can be chronic and difficult to treat.[250] Ethicon also knew of the possibility that nerve damage could cause lifelong pain.[251] If such complications as chronic pain, dyspareunia, or other complications necessitate mesh removal, the removal "can prove to be a challenge" because of tissue ingrowth, and there can be "damage to tissue during the removal process or other complications related to the removal surgery."[252] While "[i]t would have seemed very unlikely," Dr. Hinoul affirmed that Ethicon considered the risk at the time of TVT launch that "some patients would suffer complications making it impossible for them to have comfortable sexual relations for the rest of their lives."[253] Dr. Weisberg also agreed that painful sexual intercourse was a risk of the TVT device that Ethicon was aware of at the time the product was launched in the United Staes in 1998,[254] Dr. Arnaud also agreed that the fact the mesh could erode into the vagina and cause dyspareunia or painful sexual intercourse was a risk he knew about at the time of launch.[255]

As regards inflammatory reactions to the mesh foreign body, Dr. Hinoul explained why "some patients will have more major inflammatory reactions from the foreign body, the mesh, than other patients."[256] Specifically, people respond to a foreign substance differently, as with allergies. So the way people form a scar will differ and, accordingly, scarring from a TVT mesh "may differ from one patient to another."[257]

Ethicon also knew at the time of TVT launch that a patient potentially could develop worse stress urinary incontinence or have a recurrence of incontinence following TVT surgery. As Dr. Hinoul testified, "It's inherent to incontinence surgery,"[258] as is voiding dysfunction. Dr. Hinoul and Dr. Arnaud affirmed that voiding dysfunction also was a known potential complication at the time of TVT launch.[259]

Approximately two years after TVT launch, in June 2000, a GYNECARE TVT Summit Meeting was held to "create a clear, consistent, and structured approach to training."[260] The Summit Meeting was directed by Dr. Vincent Lucente, Dr. Eric Kuhn, and Dr. Carl Klutke with the intent

[247] *Id.*, 575:21-576:14.
[248] Dr. Axel Arnaud deposition, July 19, 2013, 122:3-12.
[249] Dr. Piet Hinoul deposition, June 27, 2013, 577:16-578:10.
[250] *Id.*, 577:12-14.
[251] *Id.*, 580:25-581:3.
[252] *Id.*, 578:12-579:4.
[253] *Id.*, 580:12-24.
[254] Dr. Marty Weisberg deposition, August 9, 2013, 714:1-716:3
[255] Dr. Axel Arnaud deposition, July 9, 2013, 116:21-119:9; 125:15-126:6
[256] Dr. Piet Hinoul deposition, June 27, 2013, 579:5-11.
[257] *Id.*, 579:13-21.
[258] *Id.*, 581:4-582:2.
[259] *Id.*, 582:10-583:1; Dr. Axel Arnaud deposition, July 19, 2013, 117:12-15.
[260] ETH.MESH.00658177 at 180: Surgeon's Resource Monograph – Expert opinions on the use of GYNECARE TVT Tension-Free Support for Incontinence, A REPORT of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases.

of creating a resource monograph for proctoring surgeons that defined the proper approach to GYNECARE TVT device training. The resource monograph that was developed as a result of this summit included the experience of more than 20 active proctors of the TVT system.[261] Included in the monograph is a discussion of potential complications, their causes and recommendations. The following specific complications are listed in this monograph: vaginal bleeding; retropubic hematoma; vaginal perforation during surgery; bladder perforations; inability to void after the procedure; injured urethra; urethral erosion; mesh protrusion (or defective healing); vascular injuries; bowel perforations; de novo urge and possibility of post-operative obstruction; infection of the mesh; urinary tract infection; and device failure. All of these complications are represented in the above listings and discussion of potential complications known to Ethicon at the time of TVT launch, except for one: vaginal perforation.[262]

After the FDA Public Health Notice (PHN) in 2008, Ethicon supplemented its statement of risks to patients, but never updated the risk information contained in the IFU.[263] Ethicon admitted that it knew about all complications referenced in the FDA's 2008 PHN and publically stated that all complications were already contained in its labeling.[264] Ethicon's actions thereafter support that Ethicon knew that information about serious and life changing complications associated with the TVT should be added to the labeling. Specifically, Ethicon supplemented its patient brochures (but not the IFU) to include additional risk information in late 2008, but the changes did not adequately warn of all known serious risks.[265] In early 2009, an Ethicon document reveals that employees discussed updating the IFU to include additional risk information and specifically noted "patient specific concerns", including that patients were not getting adequate risk/benefit information, concerns about erosions, about re-operations related to erosions, about dyspareunia and pain affecting patients' quality of life, and that the type and intensity of the post-operative complications were disproportionate to patients' pre-operative expectations.[266] Despite these internal discussions about updating the IFU, the IFU was not changed.

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[261] ETH.MESH.00658177 at 180: Surgeon's Resource Monograph – Expert opinions on the use of GYNECARE TVT Tension-Free Support for Incontinence, A REPORT of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases.

[262] ETH.MESH.00658177 at 189-191: *Id.*

[263] ETH.MESH.08003279: Patient Brochure-Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living (2008); ETH.MESH.08003295: Patient Brochure-Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living (2011); ETH.MESH.09744858: Patient Brochure-Stop Coping. Start Living. What You Should Know About Stress Urinary Incontinence; ETH.MESH.05225354: Instructions for Use (IFU): TVT Tension-free Vaginal Tape; ETH.MESH.02340306: Instructions for Use (IFU): Gynecare TVT Tension-free Vaginal Tape; ETH.MESH.02340471 and ETH.MESH.05222673: Instructions for Use (IFU): Gynecare TVT Tension-free Vaginal Tape; ETH.MESH.02340504: Gynecare TVT Instructions for Use (IFU); ETH.MESH.03427878: Instructions for Use (IFU): Gynecare TVT Tension-free Support for Incontinence.

[264] ETH.MESH.07937824: Emails Re: Information about FDA notification on use of mesh in pelvic surgery; ETH.MESH.02310653: Email Re: Information about FDA notification on use of mesh in pelvic surgery, with FDA Public Health Notification to Healthcare Professionals attached; ETH.MESH.01706065: The Science of "What's Left Behind"…Evidence & Follow-Up of Mesh Use for SUI, PowerPoint Presentation; ETH.MESH.00669604: Data sheets showing PFR Rankings, CH Rankings, and UH Rankings. Review of the labeling at the time of Ethicon's statements about the PHN reveal that many of the complications in the PHN were not included in Ethicon's physician or patient labeling.

[265] Section VIII.B infra; (ETH.MESH.04093117: Emails Re: TVT IFUs on tape extrusion, exposure and erosion; ETH.MESH.08003279: Patient Brochure: Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living.)

[266] ETH.MESH.04081189: AE and complication of the Slings, Meeting Agenda.

When the FDA subsequently issued an update PHN in July of 2011[267], Ethicon once again supplemented risk information in its TVT patient brochure with necessary risk information, but again chose not to make any changes to the IFU.[268] As described in Section VIII.B, these changes to the patient brochure in 2011 and again in 2012 included information about the serious, life altering complications associated with the TVT – all of which Ethicon admits it knew even at the time of launch of the TVT product.[269] This information, and more, was necessary years earlier so that physicians and patients could have all the necessary risk information needed in order to perform a fully informed risk/benefit analysis.

2. Source: FDA MAUDE Database

As discussed in detail in Section X., an independent search/review of the Manufacturer and User Facility Device Experience (MAUDE) database was undertaken for the purposes of this Report, specifically, to evaluate the relevant serious adverse event information known or knowable to Ethicon from the MAUDE database (which includes MDRs submitted by Ethicon). The first date on which an MDR was recorded in the MAUDE database for the TVT device was 1999. Tabulations of the adverse events reported between 1999 through 2010 are presented for the reader's review in Exhibit 1. An assessment of these adverse events shows that the most frequently reported complications are representative of those discussed above.

3. Source: Scientific and Medical Literature

Prior to the initial marketing of TVT in 1998,[270] the literature relevant to the use of synthetic mesh for SUI repair was limited but provides evidence that the potential for specific complications associated with use of mesh was known or knowable to Ethicon. Three reviews on the surgical management of female stress urinary incontinence and/or the use of synthetic mesh in gynecologic surgery are presented below, along with a discussion of the complications reported in the clinical evaluations provided in the TVT 510(k) Number K974098: Ulmsten et al.; Eriksson (MEDSCAND) Scandinavian multi-center trial; Drs. Wang and Lo (Taipei, Taiwan); and Dr. Blaivas and Lauri Romanzi. Individual summaries of a number of relevant publications that span the time period from 1996 (Ulmsten et al. article) through 2012 are provided in Appendix C.

3.1 Literature Reviews

In 1997, the same year in which Ethicon submitted the TVT 510(k) premarket notification to FDA, Iglesia and colleagues[271] reviewed the use of synthetic mesh materials (including polypropylene) in gynecologic surgery. There were no randomized prospective trials available; all articles reviewed consisted of sacrocolpopexy, suburethral sling, or pelvic sling retrospective case series. The authors concluded that the ideal synthetic mesh material for pelvic surgery was yet to be developed; the

[267] ETH.MESH.02253078: Emails Re: FDA Health Notification.
[268] ETH.MESH.08003295: Patient Brochure: Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living; Significant additions were added again in 2012 to the patient brochures. See Section VII.B infra.
[269] Dr. Piet Hinoul deposition, June 27, 2013, 551:12-552:9; Axel Arnaud deposition July 19, 2013, 114:21-127:1; Catherine Beath deposition July 12, 2013, 608:13-20.
[270] Dr. Piet Hinoul deposition, June 27, 2013, 551:23-552:1.
[271] Iglesia CB, Fenner DE, and Brubaker L. The use of mesh in gynecological surgery. Int Urogynecol J 1997;8:105-115.

disadvantages of synthetic mesh included *foreign-body reaction* with the risk of *infection*, *rejection*, and *erosion*. Further, the authors commented it was likely that the rate of *graft-related complications was underestimated*, because *follow-up* of patients in most studies was *limited*. It was reported that once a vaginal erosion occurred, *removal of the mesh* might be necessary for complete healing. Due to the known complications of synthetic mesh, the authors favored autologous materials as the primary choice when technically feasible. (Emphasis added.)

Also in 1997, the American Urological Association reported the results of an analysis of the literature regarding surgical procedures for treating stress urinary incontinence. The analysis was undertaken by the Female Stress Urinary Incontinence Clinical Guidelines Panel to make practice recommendations based on treatment outcomes data.[272] Outcomes data were extracted from 282 articles considered by the panel to have some type of acceptable outcomes data, following a MEDLINE database search for all articles through 1993 on surgical treatment of female stress urinary incontinence. The panel reported that the "data indicate that after 48 months retropubic suspensions and slings appear to be more efficacious than transvaginal suspensions, and also more efficacious than anterior repairs."[273] The panel also found that "retropubic suspensions and sling procedures are associated with slightly higher complication rates, including longer convalescence and postoperative voiding dysfunction."[274] Further, "[t]he literature suggests *higher complication rates when synthetic materials are used for slings*."[275] [Emphasis added.]

Among the complications reported for sling procedures were *postoperative urgency* and *urinary retention*. "The estimated probability of temporary urinary retention lasting longer than 4 weeks [was]…..8% for sling procedures."[276] For *permanent retention*, the panel found there were no accurate data at the time of their analysis. However, "[i]n the panel's opinion the risk is somewhat higher for sling procedures than for other procedures" but "the risk of permanent retention generally does not exceed 5%," regardless of procedure.[277] Other specific complications reported included *urinary tract infection*, *vaginal erosion*, *urethral erosion*, *wound infection*, *wound sinus*, *fistula*, *seroma* (one report), and *requirement for transfusion* (4% [median value]).[278] Death was reported but noted to be a rare complication of surgery for stress urinary incontinence. For considering other complications, the following general groupings were used: general medical complications; intraoperative complications, perioperative complications; subjective complications; and complications requiring surgery. For sling procedures, rates ranged from 3-12% (median values), with a 3% rate for complications requiring surgery.[279] [Emphasis added.]

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[272] Leach GE et al. Female Stress Urinary Incontinence Clinical Guidelines Panel Summary Report on Surgical Management of Female Stress Urinary Incontinence. J Urology 1997;158:875-880 [included in 510(k) Number K974098 submission].
[273] *Id.*
[274] *Id.*
[275] *Id.*
[276] *Id.* at page 877.
[277] Leach GE et al. Female Stress Urinary Incontinence Clinical Guidelines Panel Summary Report on Surgical Management of Female Stress Urinary Incontinence. J Urology 1997;158:875-880 [included in 510(k) Number K974098 submission], at page 877.
[278] *Id.*
[279] *Id.* at pages 876-877.

In a 2001 review by Cervigni and Natale[280] of the use of synthetic mesh for repair of pelvic organ prolapse (POP), in particular, for abdominal sacral colpopexy and transvaginal cystocele, a series of properties of the 'ideal' synthetic biocompatible material was presented, including, among others, that the material should be chemically and physically inert, mechanically strong, cause no allergic or inflammatory reactions, and not be physically modified by body tissue. Importantly, none of the synthetic meshes available for use met all of the 'ideal' criteria. The most frequent mesh-related complications included the following: *infection* and *sinus tract formation*; *seroma formation* caused by *inflammatory reaction* and the dead space created between the synthetic mesh and host tissue; intestinal *adhesion*; *fistula formation*; *erosion*, which was noted to be dangerous when the mesh was in direct contact with organs without serosal covering, such as the rectum, bladder, and the denuded intestinal tract; and *mesh shrinkage* by approximately 20% due to *contraction* of the mesh fibers during the *scarring* process. *Dyspareunia* and 'de novo' *stress urinary incontinence* also were reported. Although this review assessed complications of synthetic mesh used for POP repair, instead of SUI repair, it is included here because the same mesh-related complications have also been reported for the TVT device, notably in the MAUDE database.

3.2 Clinical Evaluations Provided in 510(k) Number K974098[281]

Ulmsten et al.[282] treated 75 subjects with SUI using a modified intravaginal slingplasty procedure and followed them for two years. The only complications reported included immediate *postoperative voiding problems* necessitating an indwelling catheter over the first postoperative night in five patients (6.7%) and *urinary infection* in five patients (6.7%) within 14 days after the surgery. Otherwise, the authors reported there were "[n]o significant intra- or postoperative complications [that] occurred, i.e., no patient had bleeding >300 ml and no bladder perforation occurred."[283] Dr. Margaret Eriksson,[284] Medscand Medical, summarized the results of an open, non-randomized, prospective, multicenter study of the Ulmsten procedure with the IVS device for the treatment of SUI conducted at six medical centers in Scandinavia. Dr. Eriksson noted that this recently developed surgical procedure for SUI had been used at Akademiska sjukhuset, Uppsala and at collaborating Swedish and Scandinavian centers for some years. As of May 1997, 131 subjects had been enrolled, aged 35 to 86 years (Mean 53.08 years). Subjects were followed at 2, 6, and 12 months after surgery. Complications reported included the following: *urinary retention* (four cases that resolved within one to three days); *bladder perforation* (one case); *hematoma* (one case); and *vaginal wound infection* (one case). While three of the cases of urinary retention resolved with catheterization, the fourth required intervention. "The hematoma resolved over time

[280] Cervigni M and Natale F. The use of synthetics in the treatment of pelvic organ prolapse. Curr Opinion Urol 2001;1:429-435.
[281] As stated previously herein, all the clinical data submitted in support of the 510(k) were data from studies using the IVS device, not the actual TVT device. The studies did, however, report complications associated with the use of the device.
[282] Ulmsten U et al. An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence. Int Urogynecol J 1996;7:81-86 [included in 510(k) Number K974098 submission].
[283] *Id.* at page 84.
[284] Eriksson M (MEDSCAND). Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure - Clinical Report. October 17, 1997 [unpublished report, included in 510(k) Number K974098 submission].

without treatment while the vaginal infection required surgical intervention with resection of *exposed mesh*."[285] (Emphasis added.)

Wang and Lo[286] reported on the outcomes of 70 women with SUI who were enrolled in a non-randomized, prospective study using the Ulmsten procedure and the IVS device. . Reported complications included *bladder perforations* during surgery (3) and *blood loss > 200 ml* that necessitated an indwelling catheter and vaginal tamponade in 11 subjects (16%). Note that only a one-page study summary was available in the 510(k) submission for this study. Blaivas and Romanzi[287] reported on 28 women, aged 31-70 years, with Types 1 & 2 SUI who were treated with a pubovaginal sling, specifically, a free graft of rectus fascia, passed around the urethra and tied above the rectus fascia without tension. Subjects were followed for 1 to 6 years (mean = 1.5 years). All were cured of SUI and two developed *mild de novo detrusor instability* and one had *persistent detrusor instability*.[288] (Emphasis added.)

B. Summary: TVT Known Potential Complications

Internal Ethicon documents, testimony of Ethicon employees, and reviews of the scientific and medical literature discussed above show that the potential complications listed in Table VII.1. below were known or knowable to Ethicon to be potential risks associated with synthetic mesh for SUI repair at the time of the TVT launch or by June 2000, prior to the in-use date of the first IFU available for review (September 2000).

[285] Eriksson M (MEDSCAND). Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure - Clinical Report. October 17, 1997 [unpublished report, included in 510(k) Number K974098 submission].
[286] Wang AC and Lo TS. Tension-Free Vaginal Tape (TVT) for Uinary Stres Incontinence --- A Preliminary Report [unpublished report, [included in 510(k) Number K974098 submission].
[287] Blaivas JG and Romanzi L. Pubovaginal Fascial Sling for Type 1 & 2 Stress Incontinence. Abstract, presented at the American Urological Association Annual Convention, 1996[included in 510(k) Number K974098 submission].
[288] *Id.*

Table VII.1. Known Potential Complications at TVT Launch (or by 2000 if so indicated)

POTENTIAL COMPLICATIONS		SOURCE
Erosion, extrusion, or exposure of mesh/rejection (may be recurrent; may require mesh removal and/or surgical treatment)		+
Pain		†
Chronic pain		†
Infection		+
Abscess		†
Fistula		+
Wound sinus		+
Seroma		+
Hematoma		+
Hemorrhage/potential requirement for transfusion		+
Venous thrombosis		†
Vaginal scarring		†
Shrinkage, due to contraction and scarring		†
Urinary problems		+
	Urethral obstruction	†
	Voiding dysfunction	+
	De novo detrusor instability or urgency	+
	Urinary retention (temporary or permanent)	+
	Urinary tract infection	+
	Dysuria	†
	Hematuria	†
	Worsening or recurrence of incontinence	†
Irritation at wound site		†
De novo dyspareunia		†
Inflammation, Inflammatory/foreign body reaction		+
Delayed healing		† (2000)
Complications requiring re-surgery		†
Complications requiring mesh removal		+
Nerve damage		†
Blood vessel perforation		†
Bowel perforation		†
Bladder perforation		+
Urethral injury		† (2000)
Vaginal perforation		† (2000)
Device failure		† (2000)
Death		+

† Known or knowable to Ethicon as evidenced from internal Ethicon documents and testimony.

+ Reported as complications in the literature for sling procedures to treat SUI and also known or knowable to Ethicon as evidenced from internal Ethicon documents and testimony.

VIII. INADEQUATE AND MISLEADING LABELING: MISBRANDING AND FAILURE TO WARN

A. Instructions for Use (IFU)

A medical device's professional labeling, namely, the Instructions for Use (IFU), is the cornerstone of risk management, because its purpose is to provide the physician with the necessary information to make decisions about device usage for a particular patient and then to use the device safely and effectively. Dr. Martin Weisberg, Medical Director at Ethicon since 2001,[289] acknowledged that the goal of the IFU is to communicate all of the most important safety risks attributable to the TVT device and, further, that an IFU should never exclude known hazards or complications related to the device or underestimate the risks of using the product.[290]

The failure of labeling to meet the requirements of the labeling regulations constitutes misbranding. Specifically, professional labeling (IFU) that contains misleading statements, has inadequate directions for use, and/or fails to warn about potential adverse consequences or contraindications for device use renders a device misbranded. Dr. Weisberg testified that the IFU fails in one of its principal purposes as regards known complications that are excluded or risks that are understated.[291] Such deficiencies in the TVT Instructions for Use are discussed below.

Based on the IFUs produced by Ethicon in this litigation, there were six versions of the TVT IFU, additional to the 1997 draft IFU included in the 510(k) submission, with the following in-use dates (first date of use shown): September 8, 2000[292]; December 22, 2003[293]; February 11, 2005[294]; April 7, 2006[295]; October 13, 2008 [296]; and November 29, 2010.[297]

For each of the six IFU versions, Table VIII.1. below shows the safety information provided in the IFU, specifically, adverse reactions, contraindications, warnings and precautions. If the information provided in these sections of the IFU is the same as the prior version, "Same as Previous" is indicated. Any differences in versions are indicated by gray shading. Notably, the adverse reactions and contraindications sections have remained exactly the same from the first use in September 2000 to the present (except for deletion of the word "polypropylene" after "PROLENE" in the contraindications section of the current in-use version, as indicated in Table VIII.1.). While three additions were made to the warnings and precautions in the second in-use version of the IFU (December 22, 2003), there have been no changes to the warnings and precautions since that time (except for inclusion of the word "Gynecare" preceding "TVT"). Yet Catherine Beath, Vice President of Quality Assurance and Regulatory Affairs, agreed that "a reasonably prudent medical device company would continually update the label consistent with developing data and

[289] Martin Weisberg, MD, deposition, August 9, 2013, 644:15-23.
[290] *Id.*, 959:19-960:16.
[291] *Id.*, 961:11-17.
[292] ETH.MESH.05225354-385: TVT Tension-free Vaginal Tape IFU, In use 09/08/2000-11/26/2003.
[293] ETH.MESH.02340306-369: Gynecare TVT Tension-free Vaginal Tape IFU, In use 12/22/2003-02/11/2005.
[294] ETH.MESH.02340471-503: Gynecare TVT Tension-free Vaginal Tape IFU, In use 2/11/2005-04/07/2006.
[295] ETH.MESH.05222673-704: Gynecare TVT Tension-free Vaginal Tape IFU, In use 04/07/2006-10/07/2008.
[296] ETH.MESH.02340504-567: Gynecare TVT Tension-free Support for Incontinence IFU, In use 10/13/2008-11/22/2010.
[297] ETH.MESH.03427878-945: Gynecare TVT Tension-free Support for Incontinence IFU, In use 11/29/2010-present.

information that becomes known to the company" when an update is appropriate.[298] Gregory Jones, former Director Regulatory Affairs at Ethicon, also testified that "it's important for medical device manufacturers, including Ethicon, to provide clear and accurate information to physicians and patients to avoid needless harms"[299] and "a medical device manufacturer should warn physicians about serious risks associated with their devices," agreeing that "it would be wrong for a medical device manufacturer not to warn of serious risks."[300]

[298] Catherine Beath deposition, July 11, 2013, 198:8-13.
[299] Gregory Jones deposition, August 20, 2013, 39:18-22.
[300] Gregory Jones deposition, August 20, 2013, 41:11-18.

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
Bates #	ETH.MESH. 05225354, 382-383	ETH.MESH. 02340306, 332-333	ETH.MESH. 02340471, 484-485	ETH.MESH. 05222673, 686-687	ETH.MESH. 02340504, 531-532	ETH.MESH. 03427878, 881-882
Dates: Brochure Date; First Use Date*; Last Use Date*	February 2000; September 8, 2000; November 26, 2003	August 2001; December 22, 2003; February 11, 2005	October 2004; February 11, 2005; April 7, 2006	October 2004; April 7, 2006; October 7, 2008	October 13, 2008; November 22, 2010	2009; November 29, 2010; Present
Adverse Reactions	Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair. Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation. As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination. Over correction i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.	Same as Previous	Same as Previous	Same as Previous	Same as Previous	Same as Previous

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
Contra-indications	As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the PROLENE polypropylene mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.	Same as Previous	Same as Previous	Same as Previous	Same as Previous	As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the PROLENE mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.
Warnings and Precautions	**Do not use TVT procedure for patients who are on anticoagulation therapy. Do not use TVT procedure for patients who have a urinary tract infection.** Users should be familiar with surgical technique for bladder neck suspensions before employing the TVT device. It is however important to recognize that TVT is different from a traditional sling procedure in that the tape should be located without tension	Do not use TVT procedure for patients who are on anti-coagulation therapy. Do not use 'IVT procedure for patients who have a urinary tract infection. Users should be familiar with surgical technique for bladder neck suspensions and should be adequately trained in implanting the TVT system before employing the TVT device. It is important to	Same as Previous	Same as Previous	Do not use GYNECARE TVT procedure for patients who are on anticoagulation therapy. Do not use GYNECARE TVT procedure for patients who have a urinary tract infection. Users should be familiar with surgical technique for bladder neck suspensions and should be	Same as Previous

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
	under mid-urethra. Acceptable surgical practice should be followed for the TVT procedure as well as for the management of contaminated or infected wounds. The TVT procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and proper passage of needles will minimize risks. Retropubic bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from hospital. Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should be gently pushed into the Foley catheter so that the catheter guide does not extend into the holes of the Foley Catheter. When removing the rigid catheter guide, open the handle completely so that	recognize that TVT is different from a traditional sling procedure in that the tape should be located without tension under mid-urethra. Acceptable surgical practice should be followed for the TVT procedure as well as for the management of contaminated or infected wounds. The TVT procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and proper passage of needles will minimize risks. Retropubic bleeding may occur postoperatively. Observe for any symptoms or signs before releasing patient from the hospital. Cytoscopy should be			adequately trained in implanting the GYNECARE TVT system before employing the GYNECARE TVT device. It is important to recognize that GYNECARE TVT is different from a traditional sling procedure in that the tape should be located without tension under mid-urethra. Acceptable surgical practice should be followed for the GYNECARE TVT procedure as well as for the management of contaminated or infected wounds. The GYNECARE TVT procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and	

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

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Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
	the catheter remains properly in place. Do not remove the plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with minimal tension under mid-urethra. PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material. The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Post-operatively the patient is recommended to refrain from heavy lifting and/or exercise (i.e. cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria, bleeding or	preformed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should be gently pushed into the Foley catheter so that the catheter guide does not extend into the holes of the Foley Catheter. When removing the rigid catheter guide, open the handle completely so that the catheter remains properly in place. Do not remove the plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with minimal tension under mid-urethra. PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the			proper passage of needles will minimize risks. Retropubic bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from the hospital. Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should be gently pushed into the Foley catheter so that the catheter guide does not extend into the holes of the Foley catheter. When removing the rigid catheter guide, open the handle completely so that the catheter remains properly in place. Do not remove the	

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
	other problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded. Do not contact the PROLENE mesh with any staples, clips or clamps as mechanical damage to the mesh may occur. Do not resterilize TVT device. Discard opened, unused devices.	material. The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical experience is available with vaginal delivery following the TVT procedure, in case of pregnancy delivery via cesarean section is recommended. Post-operatively the patient is recommended to refrain from heavy lifting and/or exercise (i.e. cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria, bleeding or other			plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with minimal tension under mid-urethra. PROLENE Mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material. The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical experience is available with vaginal delivery following the GYNECARE TVT procedure, in case of pregnancy delivery via cesarean section	

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
		problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded. As with other incontinence procedures, de novo detrusor instability may occur following the TVT procedure. To minimize this risk, make sure to place the tape tension-free in the mid-urethral position. Do not contact the PROLENE mesh with any staples, clips or clamps as mechanical damage			is recommended. Postoperatively, the patient is recommended to refrain from heavy lifting and/or exercise (i.e., cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria , bleeding or other problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be	

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		to the mesh may occur. Do not resterilize TVT device. Discard opened, unused devices.			corroded should not be used and should be discarded. As with other incontinence procedures, de novo detrusor instability may occur following the GYNECARE TVT procedure. To minimize this risk, make sure to place the tape tension-free in the mid-urethral position. Do not contact the PROLENE Mesh with any staples, dips or clamps, as mechanical damage to the mesh may occur. Do not resterilize GYNECARE TVT device. Discard opened, unused devices	

*Date provided by attorneys

1. Safety Information Missing from IFUs: Adverse Reactions

The "Adverse Reactions" section of medical device labeling should include all adverse reactions, or undesirable effects, reasonably associated with the use of the device, including those that are also mentioned in the "Contraindications," "Warnings," and "Precautions" sections of the labeling. As appropriate, the listing of adverse reactions should be followed by statement(s) that direct the reader to other section(s) of the labeling (e.g., Warnings) for additional information and steps to be taken in regards to the adverse reactions. Adverse reactions should be listed in the labeling according to their clinical significance, i.e., those occurring with greater severity and frequency should be listed first.[301]

From the time of launch of the TVT, the adverse reactions listed below were known or knowable to Ethicon, as discussed previously in this Report, yet were missing from the IFU. As a result, surgeons were denied both the full scope of safety information necessary to assess the potential risks of implanting the device, versus the benefit, and also information concerning potential and known adverse reactions for which patients should be monitored and managed during and after implantation. Moreover, surgeons lacked the necessary information to fully inform and consent patients regarding the potential risks of TVT implantation. As Catherine Beath, Ethicon's Vice President of Quality Assurance and Regulatory Affairs, confirmed, "physicians should be made aware of all the significant safety risks associated with the product in the IFU."[302] Medical Director Dr. Robinson also agreed that it is "important for patient safety to have all the significant risks and complications be provided to both doctors and to patients either from doctors or from information from the company."[303] According to Medical Director Dr. Martin Weisberg, Ethicon's "policy is to include any adverse events related to the device that are expected to happen on a more than occasional basis."[304] Ethicon failed to comply with that policy and fell below the standard of care required of a reasonably prudent medical device manufacturer by its failure to warn physicians of the following risks:

- Pain, including chronic pain
- Infection (Only "may potentiate an *existing* infection" is included.) (Emphasis added.)
- Abscess
- Wound sinus
- Seroma
- Hematoma
- Hemorrhage (Note that the Warnings and Precautions, however, include that "[r]etropubic bleeding may occur postoperatively" and that if bleeding should occur, "the patient is instructed to contact the surgeon immediately.")
- Venous thrombosis
- Vaginal perforation
- Vaginal scarring
- Foreign body reaction

[301] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[302] Catherine Beath deposition, July 12, 2013, 592:7-11.
[303] Dr. David Robinson deposition (rough transcript), September 11, 2013, 240:3-8.
[304] Dr. Martin Weisberg deposition, August 9, 2013, 707:19-24.

- Delayed healing
- Shrinkage, due to contraction and scarring
- Urinary problems, including:
  - Urethral injury
  - Voiding dysfunction
  - De novo detrusor instability or urgency (Note that in the IFUs in-use from 12/22/2003, the Warnings and Precautions included that "de novo detrusor instability may occur following the TVT procedure.")
  - Urinary retention
  - Urinary tract infection
  - Dysuria (Note that the Warnings and Precautions include that if dysuria should occur, "the patient is instructed to contact the surgeon immediately.")
  - Hematuria
  - Worsening or recurrence of incontinence
- De novo dyspareunia
- Complications requiring mesh removal and/or re-operation
- Device failure
- Death (Note that 15 deaths have been reported in the MAUDE database).

2. Safety Information Missing from IFUs: Warnings and Precautions

Serious adverse reactions such as those that may result in a persistent or significant incapacity or have the potential to substantially disrupt a patient's ability to conduct normal life functions should be described in the Warnings section of the labeling, in addition to those that may require medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Other clinically significant adverse reactions, e.g., those that occur frequently and have implications for patient management or may lead to a potentially serious outcome, also should be included in the Warnings section. As applicable, the description of an adverse reaction in the Warnings section also should include actions to be taken to reduce the likelihood or severity of the event and how to monitor for or manage the event.

The Warnings in the TVT IFUs from the first in-use IFU through the IFU in current use have been and are now incomplete in my professional opinion. In my professional opinion, the Warnings listed below (or similar wording) should have been included in all IFUs.

- Mesh extrusion or erosion may occur and is a persistent or lifelong risk; some will require surgical correction, and multiple surgeries may be necessary. There is the potential risk that a patient may experience chronic, unresolvable pain.
  - Dr. David Robinson testified that there is a risk of erosion "as long as the foreign body remains in place." While the IFU included erosion and extrusion as adverse reactions, there was no warning that such risk was lifelong or that patients could have multiple erosions requiring multiple surgeries, yet this was known. Further, he acknowledged that in such cases the patient's pain might never be resolved.[305]
- De novo dyspareunia may occur and be persistent.

[305] Dr. David Robinson deposition (rough transcript), September 11, 2013, 328:11-21; 329:12-330:7.

  - Dr. Robinson acknowledged the occurrence of dyspareunia (painful sexual intercourse) and that this warning does not appear in the IFU.[306]
- Erosion through the vaginal mucosa may cause irritation to the patient's intimate partner.
- The TVT is intended to be a permanent implant, but foreign body reaction and inflammation may require implant removal; complete removal may not be possible, and morbidity associated with explant may be significant.
  - Dr. Robinson agreed that he "knew at all times while [he was] the medical director, that there would be a foreign body reaction any time the mesh would go in the woman's body."[307] As long as mesh is still present, "there will be some long-term foreign body reaction to it or reaction."[308] Yet, as Dr. Robinson further testified, the IFU states only that "a transitory foreign body response may occur" (in the adverse reactions section of the IFU).[309] As Dr. Piet Hinoul testified, if complications such as chronic pain, dyspareunia, or other complication necessitate mesh removal, the removal "can prove to be a challenge" because of tissue in-growth, and there can be "damage to tissue during the removal process or other complications related to the removal surgery."[310]
- Chronic pain may result from foreign body reaction and/or scarring and contraction.
  - Dr. Robinson affirmed that Ethicon "was getting complaints related to chronic pelvic pain" and that he knew there were related data in the literature.[311] He acknowledged that "when mesh contracts, that can cause pain for patients."[312] Importantly, the extent of contraction or shrinkage is related to the intensity of the foreign body reaction; excessive foreign body reaction results in a massive scar plate and, thus, more shrinkage. There are differences among individual patients regarding the extent of foreign body reaction, i.e., there are "high and low responders."[313]
- TVT mesh has been reported to narrow, curl or deform with tension which may lead to erosion or pain for patients. Loss of pore size due to mesh narrowing or deformation may also lead to urinary retention or erosion.[314]
- TVT mesh was shown to be cytotoxic in some in vitro tests for cytotoxicity.
- The polypropylene used in the TVT mesh gave rise to local sarcomas in a study in which it was implanted in rats.

B. Patient Brochure (Patient Labeling)

A Patient Brochure was not included for FDA's review in the "Proposed Labeling" section of the initial 510(k) Premarket Notification for the TVT (K974098) nor in the subsequent 510(k)

[306] *Id.*, 330:20-331:20.
[307] Dr. David Robinson deposition (rough transcript), September 11, 2013, 275:21-25.
[308] *Id.*, 277:5-12.
[309] *Id.*, 280:5-11.
[310] *Id.*, 578:12-579:4.
[311] *Id.*, 172:18-173:3.
[312] *Id.*, 270:6-10.
[313] Powerpoint: Factors related to mesh shrinkage: What do we know? A review of literature and internal studies, by K. Spychaj, 02/23/2007 (Exhibit No. 1286, Dr. David Robinson deposition, 09/11/2013).
[314] ETH.MESH.01218019: Design FMEA TVT LCM Project; David Robinson deposition, September 11, 2013, 1079:3-7; 1081:9-13; 1083: 8-18.

submission (K012628). The information that is required in a premarket notification submission includes "Proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use."[315] The date printed on the first Patient Brochure available for review is 2001. Notably, K012628 was submitted to the FDA in August 2001 and cleared October 26, 2001.

Patient labeling is defined as any information associated with a device that is targeted to the patient (or lay caregiver), including brochures or leaflets given to and used by patients with or without accompanying professional counseling,[316] and includes Brochures on the manufacturer's website. The two general categories of information in patient labeling are risk/benefit information and instructions for use. For implants such as the TVT device, patient labeling generally consists of risk/benefit information to help patients decide whether to have a device used on them and to allow patients to become aware of potential problems with the device. Patient labeling may also include descriptive information about the device, types of patients for whom the device would not be a good choice, alternative therapeutic choices, and any other information to enable the person to make an informed decision about the device.[317] Such information is particularly important for patients with non-life-threatening conditions such as stress urinary incontinence, which, as Dr. David Robinson, Ethicon Medical Director,[318] testified is primarily a quality of life issue.[319]

In the documents available for my review, there were 14 Patient Brochures (final copy) with the following dates: 2001 (one)[320]; 2004 (one)[321]; 2005 (one)[322]; 2006 (two)[323,324]; 2007 (two)[325,326]; 2008 (two)[327,328]; 2009 (one)[329]; 2010 (two)[330,331]; 2011 (one)[332]; and 2012 (one)[333]. I also reviewed a patient video presently on the Gynecare TVT Retropubic System website. Exhibit 2 provides the risks and safety information presented in each Brochure and notes any change(s) from previous version(s).

In my professional opinion, the TVT Brochures display multiple labeling issues. First, as discussed above regarding the IFUs, many potential risks known or knowable to Ethicon were missing from

[315] 21 CFR § 807.87(e).
[316] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[317] *Id.*
[318] Dr David Robinson deposition September 11, 2013, 936:20-23.
[319] *Id.*, 132:7-10.
[320] ETH.MESH.08003173-180: GYNECARE TVT Patient Brochure 2001.
[321] ETH.MESH.08003181-196: GYNECARE TVT Patient Brochure 2004.
[322] ETH.MESH.08003197-212: GYNECARE TVT Patient Brochure 2005.
[323] ETH.MESH.08003231-246: GYNECARE TVT Family of Products Patient Brochure 2006.
[324] ETH.MESH.08003215-230: GYNECARE TVT Family of Products Patient Brochure 2006.
[325] ETH.MESH.08003247-262: GYNECARE TVT Family of Products Patient Brochure 2007.
[326] ETH.MESH.08003263-278: GYNECARE TVT Patient Brochure 2007.
[327] ETH.MESH.03458123-138: GYNECARE TVT Family of Products Patient Brochure 2008.
[328] ETH.MESH.08003279-294: GYNECARE TVT Family of Products Patient Brochure 2008.
[329] ETH.MESH.08003303-318: GYNECARE TVT Family of Products Patient Brochure 2009.
[330] ETH.MESH.06087471-472: GYNECARE TVT Patient Brochure 2010.
[331] ETH.MESH.06087513-514: GYNECARE TVT Patient Brochure 2010.
[332] ETH.MESH.08003295-302: GYNECARE TVT Family of Products Patient Brochure 2011.
[333] ETH.MESH.05815791-802: GYNECARE TVT Family of Products Patient Brochure 2012.

the Patient Brochures, although all Brochures included a section about "What are the risks," except for the two 2010 Patient Brochures. The latter were a different style (one-page, two-sided) and appear to have been designed simply to raise awareness about the TVT device and elicit interest, whereas all the other Brochures provided substantial information, for example, information on stress urinary incontinence, treatment options, how TVT differs from other options, etc. Except for the 2012 Brochure, all "What are the risks" sections began with a statement that all surgical (or medical) procedures present risks (or some risks). Table VIII.2. below shows the risk information provided in each Brochure.

Note that attached to or included with all Brochures was product safety information (adverse reactions, warnings and precautions, and/or contraindications) that was substantially the same as or an abbreviated version of the information in the professional labeling (package insert/IFU). Such product information included material that (i) is relevant only to the surgeon and not to the patient, (ii) is written in technical language that the lay patient would not be expected to understand, and (iii) is in a much smaller print size than the print used for the remainder of the Brochure, which downplays its significance. In my professional opinion, the presentation of this information did not accomplish the purpose of patient labeling, which is to provide information on the proper use, risks, and benefits of the device in language the patient can understand. Ethicon agrees with my opinion in this regard as Susan Lin, Ethicon's designated regulatory corporate representative, testified that the product information attached to the brochures was not intended for patients and was not written in lay language that could be understood by patients.[334] Yet, there appears to have been no attempt to translate the information in the professional labeling of relevance to the patient into layman's language. Nor was the safety information complete, as has been discussed above regarding the IFUs. Yet all Patient Brochures through 2009 instructed the patient to see the attached product information for a "complete description of risks."

[334] Susan Lin deposition, May 2, 2013 687:25-689:2

Table VIII.2. Risk Information Included in Patient Brochures: 2001-2012

Patient Brochure Date of Printing	Risks Provided
2001	Complications rare - Injury to blood vessels of pelvic sidewall and abdominal wall - Difficulty urinating - Bladder and bowel injury
2004	Same as 2001
2005	Same as 2001
2006 ETH.MESH.08003231 at 244	As with all procedures of its type - Risk of injury to bladder and surrounding organs
2006 ETH.MESH.08003215at 228	Same as other 2006 Brochure
2007 ETH.MESH.08003247 at 260	Same as 2006
2007 ETH.MESH.08003263 at 276	Same as 2006
2008 ETH.MESH.03458123 at 136	Same as 2006
2008 ETH.MESH.08003279 at 292	- Injury to blood vessels of the pelvis - Difficulty urinating - Pain - Scarring - Pain with intercourse - Bladder and bowel injury - Risk of mesh material becoming exposed, requiring treatment
2009	Same as 2008 (ETH.MESH.08003279 at 292)
2011	- Injury to blood vessels of the pelvis - Nerve damage - Difficulty urinating - Pain with intercourse - Bladder or bowel injury - Risk of mesh material becoming exposed into the vaginal canal -- Can be associated with pain during intercourse for patient and her partner -- May require treatment such as vaginal medication or removal of exposed mesh, either in office or operating room - Synthetic mesh is a permanent medical device implant. -- Carefully discuss decision to have surgery with your doctor. -- Understand benefits and risks of mesh implant surgery before deciding how to treat your condition.

Table VIII.2. Risk Information Included in Patient Brochures: 2001-2012 (contd.)

Patient Brochure Date of Printing	Risks Provided
2012	Risks Common to All Pelvic Surgeries: - Pain with intercourse - Pelvic pain - Development of urinary incontinence or voiding difficulties - Hemorrhage (bleeding) or hematoma (collections of blood in the pelvis) - Injury to abdominal organs including bowel - Urinary tract infection - Bladder injury - Wound healing problems - Fistula (holes between bladder or bowel and the vagina) - Injury to ureters (tubes bringing urine from kidneys to bladder) - Pelvic abscess formation - Nerve damage Complications Associated with Synthetic Mesh: - Risk of mesh material becoming exposed into the vagina -- Can be associated with pain during intercourse for patient and her partner -- May require treatment such as vaginal medication or removal of exposed mesh, either in office or operating room - Infection - Inflammation - Vaginal scarring and mesh contracture (mesh shortening due to scar tissue) - Pelvic pain (may occur and may resolve with time) - Pain with intercourse (may occur and may resolve with time) - Urinary incontinence - Difficulty urinating - Synthetic mesh is a permanent medical device implant. -- Carefully discuss decision to have surgery with your doctor. -- Understand benefits and risks of mesh implant surgery before deciding how to treat your condition.

The above table shows that it was not until 2012 that the Patient Brochure informed patients of the majority of potential risks of TVT implantation, yet all these risks were known or knowable to Ethicon at the time of product launch, as discussed above and delineated in Table VII.1. Still in 2012, there were missing risks, including the following: irritation at the wound site, wound sinus, seroma; additional urinary problems, including hematuria, urethral injury or obstruction, urgency, temporary or permanent urinary retention; vaginal perforation; blood vessel perforation [notably, included in the 2001, 2004, 2005, 2008 (one of two), 2009, and 2011 Brochures]; venous thrombosis; complications additional to mesh exposure that might require mesh removal and/or surgical correction; death, e.g., in the event of bowel perforation. Prior to 2012, the Patient

Brochures informed patients of as few as 3% and no more than approximately 20% of the known or knowable risks at the time of TVT launch, according to the information provided in Table VII.1. Although Brochures began advising patients that the mesh is a permanent implant from 2008 (one of two 2008 Brochures[335]) and thus the patient "should carefully discuss the decision to have surgery with [her] doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat [her] condition,"[336] no Brochure ever communicated that surgery to remove the mesh, if necessary because of complications, might prove challenging as a result of tissue in-growth and could cause significant morbidity. While referring the patient to her doctor for discussion of benefits and risks was appropriate, it does not replace also including known potential complications and consequences of TVT device implantation in the Brochure. Moreover, as discussed above regarding the IFU, the safety information provided in the professional labeling was incomplete and failed to provide the physician with all the necessary information to conduct a fully informed discussion of the product benefits and risks with the patient.

Additionally, the TVT Patient Brochures lacked fair balance. Risk and benefit information is to be presented in a balanced way in patient labeling and is intended to inform without any attempt to influence the patient.[337] The overriding message of the Brochures is first defined by their tag lines:

- Freedom From Stress Urinary Incontinence - It's within your control.[338]
- Stress Urinary Incontinence in Women – What YOU can do about it…[339,340]
- The Choice to End Stress Urinary Incontinence – Find out how to stop urine leakage like Bonnie did[341,342,343,344]
- The Choice to End Stress Urinary Incontinence – **One day** you have urine leakage. The next day you don't. **End of story.**[345]
- Treatment Options for Stress Urinary Incontinence – Stop coping. Start living.[346,347,348]
- Stress Urinary Incontinence - Stop coping. Start living.[349]
- Stop Coping. **Start Living**. What You Should Know About **Stress Urinary Incontinence.**[350]

Additionally, in each of the Brochures (except the two 2010 Brochures), there are five to eight photos depicting women as happy, active, and smiling with a male partner or friends, and an

[335] ETH.MESH.08003279 at 292: GYNECARE TVT Family of Products Patient Brochure 2008.
[336] *Id.*
[337] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[338] ETH.MESH.08003173: GYNECARE TVT Patient Brochure 2001.
[339] ETH.MESH.08003181: GYNECARE TVT Patient Brochure 2004.
[340] ETH.MESH.08003197: GYNECARE TVT Patient Brochure 2005.
[341] ETH.MESH.08003231: GYNECARE TVT Family of Products Patient Brochure 2006.
[342] ETH.MESH.08003215: GYNECARE TVT Family of Products Patient Brochure 2006.
[343] ETH.MESH.08003247: GYNECARE TVT Family of Products Patient Brochure 2007.
[344] ETH.MESH.03458123: GYNECARE TVT Family of Products Patient Brochure 2008.
[345] ETH.MESH.08003263: GYNECARE TVT Patient Brochure 2007.
[346] ETH.MESH.08003279: GYNECARE TVT Family of Products Patient Brochure 2008.
[347] ETH.MESH.08003303: GYNECARE TVT Family of Products Patient Brochure 2009.
[348] ETH.MESH.08003295: GYNECARE TVT Family of Products Patient Brochure 2011.
[349] ETH.MESH.06087471: GYNECARE TVT Patient Brochure 2010.
[350] ETH.MESH.05815791: GYNECARE TVT Family of Products Patient Brochure 2012.

engaged physician. There are multiple benefit messages about the TVT or TVT family of products, particularly noticeable beginning with the 2004 version, which includes the messages shown below:

- Safe and effective minimally invasive procedures…[351]
- Most reliable, permanent results[352]
- Simpler, much less invasive than traditional surgical procedures…[353]
- …*take the next step* and talk with your doctor or other healthcare professional[354] (Emphasis added.)
- Innovative, minimally invasive 30-minute, outpatient treatment
- Proven results for the effective treatment of stress urinary incontinence[355]
- Clinically proven, safe and effective[356]
- Permanent material that will be well tolerated by your body[357]
- It will be there to help support your urethra for the rest of your life[358]
- Very little or no discomfort after the procedure[359]

By contrast, only after all the above positive messages have been presented is there a single, 6-line paragraph on risks that advises the patient that all medical procedures present risks and lists a few complications, after stating they are rare.

Subsequent Brochures communicated the same or similar multiple benefit messages as those listed above, including also such messages as the following:

- Only treatment of its type with demonstrated long-term (or the longest term) clinical results – clinically proven, safe and effective[360,361]
- Only procedure of its type with 7 years of proven results – clinically proven, safe and effective[362]
- 98% of women treated with GYNECARE TVT are still dry or report significantly less leakage seven years after treatment[363,364,365,366]

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[351] ETH.MESH.08003181at 183: GYNECARE TVT Patient Brochure 2004.
[352] *Id.*
[353] *Id.*
[354] ETH.MESH.08003181at 187: *Id.*
[355] ETH.MESH.08003181at 190: *Id.*
[356] ETH.MESH.08003181at 191: *Id.*
[357] ETH.MESH.08003181at 192: *Id.*
[358] ETH.MESH.08003181at 192: *Id.*
[359] ETH.MESH.08003181at 194: *Id.*
[360] ETH.MESH.08003215 at 216: GYNECARE TVT Family of Products Patient Brochure 2006.
[361] ETH.MESH.03458123 at 133: GYNECARE TVT Family of Products Patient Brochure 2008.
[362] ETH.MESH.03458123 at 124: *Id.*
[363] ETH.MESH.08003215 at 216, 225: GYNECARE TVT Family of Products Patient Brochure 2006.
[364] ETH.MESH.08003231 at 232, 241: GYNECARE TVT Family of Products Patient Brochure 2006.
[365] ETH.MESH.08003247 at 248: GYNECARE TVT Family of Products Patient Brochure 2007.
[366] ETH.MESH.03458123 at 124, 133: GYNECARE TVT Family of Products Patient Brochure 2008.

- 97% of women surveyed following treatment with GYNECARE TVT™ were still dry or had significantly less leakage 11 years later! These women were so satisfied…that 97% said they would recommend the procedure with GYNECARE TVT™ to a friend[367,368]
- Demonstrated proven results for effectively treating stress urinary incontinence for over 11 years[369]
- Used on (or used to treat) more than 1 million women worldwide, more than any other treatment of its type[370,371,372]
- With over 1.5 million women treated worldwide, GYNECARE TVT™ is clinically proven safe and effective[373]
- Recovery is quick….back to your normal routine in just a day or two[374] or back to regular routine shortly[375]
- GYNECARE TVT…stop[s] urine leakage the way your body was designed to…[376,377,378] or designed to stop involuntary leakage the way your body should[379] or normally should[380]
- Rate of complications with GYNECARE TVT is very low[381,382]
- Rate of complications is low and most patients expect a short recovery period[383,384]
- …GYNECARE TVT, the #1 doctor-preferred treatment of its type[385]
- You don't have to suffer with it. Use this brochure to…learn about safe, effective, minimally invasive treatments[386]
- Minimal or no (or minimal) scarring and should not feel the mesh once it has been placed[387,388]
- …there are treatments that could reduce urine leakage or stop it altogether, so you can get back to doing the things you enjoy most[389]
- **All mesh is NOT created equal.** GYNECARE TVT™ is the most commonly studied procedure using mesh for SUI repair; and a substantial number of clinical trials have been published…..proven evidence of safety and effectiveness[390]

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[367] ETH.MESH.08003279 at 291: GYNECARE TVT Family of Products Patient Brochure 2008.
[368] ETH.MESH.08003303 at 315: GYNECARE TVT Family of Products Patient Brochure 2009.
[369] ETH.MESH.05815791 at 796: GYNECARE TVT Family of Products Patient Brochure 2012.
[370] ETH.MESH.08003215 at 216: GYNECARE TVT Family of Products Patient Brochure 2006.
[371] ETH.MESH.08003247 at 248: GYNECARE TVT Family of Products Patient Brochure 2007.
[372] ETH.MESH.03458123 at 124: GYNECARE TVT Family of Products Patient Brochure 2008.
[373] ETH.MESH.08003295 at 301: GYNECARE TVT Family of Products Patient Brochure 2011.
[374] ETH.MESH.08003215 at 225: *Id.*
[375] ETH.MESH.03458123 at 133: GYNECARE TVT Family of Products Patient Brochure 2008.
[376] ETH.MESH.08003215 at 226: *Id.*
[377] ETH.MESH.08003279 at 288: GYNECARE TVT Family of Products Patient Brochure 2008.
[378] ETH.MESH.08003303 at 312: GYNECARE TVT Family of Products Patient Brochure 2009.
[379] ETH.MESH.08003295 at 300: GYNECARE TVT Family of Products Patient Brochure 2011.
[380] ETH.MESH.05815791 at 798: GYNECARE TVT Family of Products Patient Brochure 2012.
[381] *Id.*
[382] ETH.MESH.08003231 at 242: GYNECARE TVT Family of Products Patient Brochure 2006.
[383] ETH.MESH.08003279 at 291: GYNECARE TVT Family of Products Patient Brochure 2008.
[384] ETH.MESH.08003303 at 315: GYNECARE TVT Family of Products Patient Brochure 2009.
[385] ETH.MESH.08003215 at 228: GYNECARE TVT Family of Products Patient Brochure 2006.
[386] ETH.MESH.03458123 at 125: GYNECARE TVT Family of Products Patient Brochure 2008.
[387] ETH.MESH.08003295 at 300: GYNECARE TVT Family of Products Patient Brochure 2011.
[388] ETH.MESH.05815791 at 800: GYNECARE TVT Family of Products Patient Brochure 2012.
[389] ETH.MESH.05815791 at 792: GYNECARE TVT Family of Products Patient Brochure 2012.
[390] ETH.MESH.05815791 at 797: GYNECARE TVT Family of Products Patient Brochure 2012.

- **Gynecare TVT™ is the gold standard in suburethral slings**
  - Studied in more women than other suburethral slings on the market
  - Studied longer than any other sling in the market
  - 97% of women experience little or no leakage…
  - More than 2 million patients have been treated worldwide[391]

Importantly, such statements in the Brochures that "98% of women treated are still dry or report significantly less leakage seven years after treatment" and "97% of women experience little or no leakage…" are misleading. As presented, these statements imply that Ethicon has outcome information for all women implanted with the TVT device, yet the source of this percentage is the seven-year follow-up of patients enrolled in the original Ulmsten et al. 1996 study.[392,393] Thus, these statements are based on clinical evaluation of only 64 women and telephone evaluation of another 16, for a total of only 80 women on which such global statements are based. It is further important to note that these statements are followed by a statement that TVT has been used to treat more than 1 million women worldwide, thus giving the appearance to the reader that 980,000 women have been successfully treated with TVT. There is no mention of such studies as the Ward and Hilton prospective multicenter evaluation[394] of the TVT versus colposuspension, in which 175 patients randomized to TVT treatment showed an objective cure of *66%* or the Barber et al. study[395] in which *79%* of 88 patients randomized to TVT (versus 82 patients randomized to transobturator tape) reported their bladder symptoms were either "much better" or "very much better" one year after study. (Emphasis added.)

Additionally, such statements as "[r]ate of complications with GYNECARE TVT is very low," or low, are misleading. For example, Jeffrey et al.[396] retrospectively evaluated 112 consecutive women treated with the TVT procedure at a single hospital in Paris in February 2000 and found that 32.1% experienced early postoperative complications, including the following: voiding difficulties lasting > 15 days (12.5%); urinary infection (10.7%); urinary retention (8%). Late postoperative complications occurred in 29.4% of patients, including de novo urge symptoms (25.9%) and voiding difficulties lasting > 15 days (3.6%). Bodelsson et al.[397] reported perioperative bladder or urethral perforation in 26 (15%) of 177 patients who underwent the TVT procedure at Malmo University Hospital, Sweden. Karram et al.[398] reported 19 bladder perforations in 17 (4.9%) of 350 consecutive patients treated with the TVT by one surgeon at Good Samaritan Hospital, University of Cincinnati Medical School from November 1997 to November 2001. Abouassaly et al. reported complications of TVT surgery based on a retrospective multi-

[391] ETH.MESH.05815791 at 798: GYNECARE TVT Family of Products Patient Brochure 2012.
[392] Ulmsten U et al. An ambulatory surgical procedure under local anesthetic for treatment of female urinary incontinence. Int Urogynecol J 1996;7:81-86.
[393] Dr. David Robinson deposition (rough transcript), September 11, 2013, 208:10-22.
[394] Ward K and Hilton P. Prospective multicentre randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002;325:1-7.
[395] Barber MD et al. Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence. Obstet Gynecol 2008;111:611-621.
[396] Jeffry L et al. Objective and subjective cure rates after tension-free vaginal tape for treatment of urinary incontinence. Urology 2001;58:702-706.
[397] Bodelsson G et al. Short term complications of the tension free vaginal tape operation for stress urinary incontinence in women. BJOG 2002;109:566-569.
[398] Karram MM et al. Complications and untoward effects of the tension-free vaginal tape procedure. Obstet Gynecol 2003;101:929-932.

institutional review performed by a single urologist of 241 patients at six hospitals (two university and four community hospitals). Among the complications were blood loss > 250 mL (13 patients, 5.4%) and bladder perforation (14 patients, 5.8%) intraoperatively. Post-surgical complications included urinary retention in 47 patients (19.5%): < 48 hours – 32 patients; > 48 hours – 15 patients. Of the patients with long-term retention, seven required TVT release and three required sectioning of the TVT [10 patients total (4.1%) requiring TVT release or sectioning]. At the one-year follow-up, there were 33 cases (13.6%) of de novo urge and 15 (6.2%) patients with mild but persistent suprapubic discomfort and 25 (10.4%) who reported at least one urinary tract infection within three months after surgery. As discussed above, Barber et al.[399] randomized 170 patients to treatment with TVT (88 patients) or transobturator tape (82 patients) to test the hypothesis that the latter approach, the purpose of which was to reduce the risk of bladder, bowel and iliac vessel injury, is not inferior to TVT. The authors note that despite its proven efficacy, the TVT is associated with rare but serious, and in some cases life-threatening, complications and is associated with a 3-9% bladder perforation rate. Study complications included, among others, mesh erosions in five (5.7%) TVT patients and abnormal bladder function (incontinence symptoms of any type; positive cough stress test; retreatment for SUI; or postoperative urinary retention) in 46.6% of TVT patients. New or worsening urge incontinence was noted after surgery in 10% of the TVT group. Rates of complications cited in these publications show that it was misleading to tell prospective patients that rate of complications is very low (or low). Even today, the patient video currently on the TVT Retropubic System website informs prospective patients that complications are rare.

For the reasons stated, the Patient Brochures failed to convey a true overview of the risks versus the benefits. Thus, the TVT Brochures failed to serve the expected intent of patient labeling, i.e., to provide factual and balanced information to aid the patient in deciding whether to have the device implanted or to select an alternative course of SUI management. The patient labeling conveyed a false and misleading impression by its failure to inform the patients of relevant information and potential risks and consequences of TVT implantation. Under Section 502 of the FDCA, this constituted misbranding. In my professional opinion, the TVT Patient Brochures fell below the industry standard of care.

Additionally, the 2012 Brochure constituted misbranding, in my professional opinion, as a result of conveying an impression of official FDA approval of the TVT device. Specifically, the Brochure noted that the patient "may be aware that in 2011 the FDA issued a safety communication concerning complications associated with surgical mesh used for pelvic organ prolapse repair." The patient was advised that "[m]esh used for pelvic organ prolapse repair is a different procedure than the mesh used to treat SUI. One type of SUI treatment is getting further scrutiny from the FDA, which is single incision slings. It is a different procedure that those used for GYNECARE TVT™ Retropubic…" The statement that constitutes misbranding followed next: "GYNECARE TVT™ Retropubic….[is] used to treat SUI, and the safety and efficacy of [this device] met the criteria for retropubic…slings established by the FDA."[400] According to 21 CFR 807.97, "[a]ny representation that creates an impression of official approval of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding."

[399] Barber MD et al. Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence. Obstet Gynecol 2008;111:611-621.
[400] ETH.MESH.05815791 at 797: GYNECARE TVT Family of Products Patient Brochure 2012.

It is the manufacturer's responsibility to ensure that professional labeling and patient labeling are consistent. My review of the IFUs and Patient Brochures, as discussed above, shows there was never complete consistency between these two forms of labeling. Ethicon significantly improved the risk information in the 2012 Patient Brochure, after having made some improvements beginning in 2008. It is notable that the risk information in the 2012 Brochure generally exceeded the risk information in the IFU, yet there remained information in the IFU that was not included in the 2012 Patient Brochure as well as vice versa. Both professional and patient labeling remained deficient as regards failure to warn of all potential known or knowable risks. It is further noteworthy that the risk of pain, vaginal scarring and shrinkage due to scarring and contraction, dyspareunia, incontinence, voiding dysfunction, urinary tract infection, abscess and wound healing appeared in the 2012 Patient Brochure but never appeared in the IFU, including the one in current use.

OPINION #2: TVT System Misbranded Due to Failure to Warn

Product labeling is a cornerstone of risk management. Its purpose is to provide the user with the information necessary to use the product safely and effectively. While labeling for prescription devices is premised on the concept that prescription devices are not safe for use except under the supervision of a licensed practitioner and, accordingly, are exempt from the "adequate directions for use" requirements applicable to over-the-counter (OTC) devices,[401] prescription device labeling nevertheless is required to contain information adequate for a licensed practitioner to use the device safely and effectively for its intended use.[402] Required use information includes indications, effects, routes, methods, and any relevant hazards, contraindications, side effects, and precautions under which the device can be used safely.[403]

Ethicon marketed the TVT System without adequate instructions for use, in particular, without adequate warnings and information about potential risks, throughout the life of the product, based on my review of the TVT IFU and patient labeling information discussed above. As the testimony of Ethicon employees and documentation and information discussed in this Report demonstrate, the company knew or should have known of the above-discussed multiple risks associated with the TVT System that were not included in the IFU and patient labeling information. Nor did the patient labeling show fair balance of benefit vs. risk information. Section 502 of the FDCA contains provisions on misbranding and the labeling issues that cause a product to be misbranded. Labeling issues that cause a device to be misbranded include labeling that is false or misleading in any particular[404] and labeling that does not bear adequate directions for use, including adequate warnings.[405] In my professional opinion, Ethicon deviated from the standard of care required of a medical device manufacturer by marketing a product that was misbranded because of the stated multiple labeling deficiencies.

[401] 21 CFR § 801.109.
[402] 21 CFR § 801.109(c).
[403] 21 CFR § 801.109(d).
[404] FDCA § 502(a), 21 U.S.C. § 352(a).
[405] FDCA § 502(f)(2).

C. Promotional Labeling

Promotional labeling is generally considered any labeling other than the professional labeling or FDA-approved labeling. Such labeling must not be false or misleading or omit material information. Following is a discussion of representative examples of promotional pieces that were false and misleading and failed to present material facts. They constituted misbranding and also reflect an absence of concern for patient safety. Notably, in determining whether labeling is misleading, "there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling…fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling….relates under the conditions of use prescribed in the labeling…thereof or under such conditions of use as are customary or usual."[406]

1. "5 Years of Proven Performance" Marketing Piece

Ethicon developed and provided this TVT marketing piece, titled "5 Years of Proven Performance," to physicians for them to see the five-year results of the Ulmsten/Nilsson study.[407] It is misleading in a number of ways. For example, physicians are not informed that the sling used in this study with five years of follow up was the IVS device and not the actual TVT device. Further, there is not a statement anywhere in the marketing piece that identifies the conflict of interest that Professor Ulmsten and Professor Nilsson have due to the fact that Professor Ulmsten was paid millions of dollars by Ethicon (including that the company he was an owner of was paid if, and only if, it could product positive safety results in a study) and Professor Nilsson was paid a substantial amount as a consultant as well.[408] In addition, this marketing piece reports that the "Urethral erosion rate $\leq$ that of traditional slings" and cites a publication which, according to the bibliography in the document, was published in 2001, but the remainder of the reference information matches to the 1997 publication by Leach et al. regarding the "Female Stress Urinary Incontinence Clinical Guidelines Panel Summary Report on Surgical Management of Female Stress Urinary Incontinence." In contrast to the information reported in the marketing piece, this publication shows *more* urethral erosion with synthetic slings, specifically, 2% urethral erosion rate for synthetic materials in contrast to an absence of urethral erosions for homologous materials and 0.3% urethral erosion rate for autologous materials. The marketing piece also notes there were "no reported urethral erosions in 10 clinical studies of 50+ patients." The 10 studies referenced included more than 1,440 patients, similar to the number of patients (1,515) reported in the Leach et al. summary report who were treated with synthetic mesh, but in the Leach et al. article, to which Ethicon cited as discussed above, there were 27 patients (2%) with urethral erosion reported.[409]

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[406] FDCA § 201(n); 21 U.S.C. 321n).
[407] Dr. David Robinson deposition (rough transcript), September 11, 2013, 201:21-25; 202:7-203:14; 204:24-205:21.
[408] ETH.MESH.09746948: License Agreement between Johnson & Johnson International and Medscand Medical A.B.; ETH.MESH.09748308 at ETH.MESH.09748316: Letter Re: Acquisition of Assets related to the Tension free Vaginal Tape (TVT); Laura Angelini deposition, September 16, 2013, 216:6-12; 216:8-15, 272:27-274:5. It is my understanding that Ethicon claims that it is unable to locate evidence of payments to consultants including Pr. Ulmsten and Pr. Nilsson prior to 2003 and, thus, the amount of the payments is likely greater than currently known. Laura Angelini deposition September 16, 2013, 287:21-288:1; 331:23-334:3.
[409] ETH.MESH.00339437 at 438: GYNECARE TVT Marketing Piece titled "5 Years of Proven Performance," 2002.

Further, this marketing piece represents to the physician that there is "no foreign body reaction after PROLENE mesh implantation." The reference given for this statement was a single article in which connective tissue metabolism was evaluated two years after Prolene implantation in 10 women and Mersilene implantation in six women, using the TVT procedure. A minimal inflammatory reaction was found in the Prolene group, while Mersilene resulted in a significant foreign-body reaction two years after implantation.[410] Yet, as discussed previously in this Report, foreign body reaction was expected[411] and, as Dr. Hinoul testified, Ethicon knew "some patients will have more major inflammatory reactions from the foreign body, the mesh, than other patients."[412] Moreover, Dr. Hinoul acknowledged that the foreign body response can cause mesh exposure and mesh erosion.[413] To advise physicians that the TVT mesh has no foreign body reaction based on the described study of 10 patients evaluated only once two years after implantation was disingenuous and misleading.

2. "Only GYNECARE TVT has Long-term Results You Can See…and Believe" Marketing Piece

Similar to the "5 Years of Proven Performance" marketing piece discussed above, the marketing piece titled "Only GYNECARE TVT has Long-term Results You Can See…and Believe" reports that there were "[n]o reported urethral erosions in multiple clinical studies of 50+ patients," citing the same references as cited in the "5 Years of Proven Performance" piece, but this new marketing piece was dated two years later (2004).[414] By contrast, a 2004 review by Bhargava and Chapple of the literature dated 1995 to 2004 on the complications of synthetic suburethral slings, including TVT, reported sling erosion to be one of the most frequently and potentially serious complications with the use of synthetic slings. While the introduction of newer sling materials such as TVT (and SPARC) appeared to have reduced the incidence of erosion, recent studies were noted to report incidences between 0.3% and 4.4%.[415]

This marketing piece also states there is a "[l]ow incidence of serious reported complications, <0.01%" (based on internal data on file).[416] Yet the literature review by Bhargava and Chapple[417] showed de novo urgency reported in 6-15% of patients undergoing TVT and urinary retention rates after TVT ranging generally from 2% to 9%, in addition to the erosion rates cited above and bladder perforation, which was reported as the most frequent intraoperative complication of TVT placement. Abouassaly et al.[418] reported a bladder perforation rate of 5.8% in a review of 241

[410] Falconer C et al. Influence of Different Sling materials on Connective Tissue Metabolism in Stress Urinary Incontinent Women. Int Urogynecol J 2001;Suppl 2:S19-S23.
[411] Dr. Piet Hinoul deposition, June 27, 2013, 565:13-21.
[412] *Id.*, 579:5-11.
[413] *Id.*, 566:1-6.
[414] ETH.MESH.00658058 at 059: GYNECARE TVT Marketing Piece titled "Only GYNECARE TVT Has Long-term Results You Can See…and Believe," 2004.
[415] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.
[416] [416] ETH.MESH.00658058 at 059: GYNECARE TVT Marketing Piece titled "Only GYNECARE TVT Has Long-term Results You Can See…and Believe," 2004.
[417] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.
[418] Abouassaly et al. Complications of tension-free vaginal tape surgery: a multi-institutional review. BJU Int 2004;94:110-113.

patients. The reported rates in the literature vary between 0 and 25%.[419] Ward and Hilton[420] reported a total complication rate of 39% (excluding fever) for tension-free vaginal tape in a comparative trial versus colposuspension as primary treatment for stress incontinence. Among the complications were bladder injury (9%), vaginal perforation (3%), wound infection (2%), retropubic hematoma (2%), vascular injury (1%), tape erosion (1%), and urinary tract infection (in six weeks after surgery, 22%).

In regards to the internal complication rate Ethicon reported as <0.01%, the following response to a communication sent to preceptors is noteworthy. Specifically, preceptors were provided "a copy of the latest complication data for GYNECARE TVT" that was "based on 900,000 patients treated worldwide."[421] Complication rates reported ranged from 0.001% to 0.006%., shown in the final column on the complications chart.[422] Dennis Miller replied: "It's fantastic to know that TVT…[is] still so safe, even with more surgeons participating..I know that all companies make these tables with the same format from the MAUDE database, but all surgeons know that the final column is a farce. Surgeons all over the country discuss it regularly. *Placing a percentage on the chart that is based on an entirely false denominator is quite misleading.*"[423] (Emphasis added.)

It is further noteworthy that in this same marketing piece, the results of the Ward and Hilton study are presented, touting that "[a] multicenter, comparative trial of women with SUI randomized to treatment with GYNECARE TVT or colposuspension found no significant difference in cure rates between the 2 groups." The data presented, however, conflict with the data presented on the prior page of the marketing piece regarding the Nilsson 7-year follow-up of the TVT procedure. The latter, just as presented in the Patient Brochures discussed above, reports a 97% overall success rate.[424] The Ward and Hilton study data presented show a 6-month cure rate of 66% for Gynecare TVT and 57% cure rate for colposuspension, with 2-year cure rates of 63% and 51% for Gynecare TVT and colposuspension, respectively.[425] Finally, this marketing piece also cites often to the Ulmsten/Nilsson studies, but physicians are not informed about the conflict of interest associated with the Ulmsten and Nilsson studies or that such studies used a different device than the TVT, as stated above.

3. "Dependability - GYNECARE TVT™ Family of Products Tension-free Support for Incontinence" Marketing Piece

The marketing piece entitled "Dependability - GYNECARE TVT™ Family of Products Tension-free Support for Incontinence" dated 2010 reports that not a single case of tape erosion, tissue reactions, or other adverse effects of the tape were found in a clinical study at an average of 11.5

[419] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.
[420] Ward K and Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002;325:1-7.
[421] ETH.MESH.00134498: Email series January 13-15, 2006, RE: GYNECARE TVT Latest Complication Data.
[422] No Bates number: Ethicon, Inc. Complaint Reporting Statement – Gynecare TVT* Tension-free Support for Incontinence, based on 900,000 patients treated worldwide. [Note that data cut-off for deaths (10) is reported as November 15, 2005].
[423] ETH.MESH.00134498: Email series January 13-15, 2006, RE: GYNECARE TVT Latest Complication Data.
[424] ETH.MESH.00658058 at 059: GYNECARE TVT Marketing Piece titled "Only GYNECARE TVT Has Long-term Results You Can See…and Believe," 2004.
[425] ETH.MESH.00658058 at 060: *Id.*

years.[426] This is referring to the 11.5 year follow up of the Ulmsten/Nilsson study that was performed with the IVS device by Professor Ulmsten, Professor Nilsson and others. Again, however, this marketing piece does not inform physicians that the device used in the study with 11.5 years of follow up was the IVS, not the actual TVT device and, further, about the substantial conflict of interest that the authors have, as stated more fully above.[427] In addition, the information in the piece does not reveal that only 77% of the original cohort of 90 women were assessed 11.5 years after the TVT operation, and only 59% (53 patients) of the original 90 were available and seen in the clinic for evaluation; the other 16 were assessed outside the clinic by interview.[428] The appropriate, accurate presentation of the data would have been a statement such as the following: "Fifty-three (59%) of 90 patients were available for clinical assessment 11.5 years after TVT surgery and showed no evidence of tape erosion, tissue reactions, or other adverse effects at this time interval post surgery; 16 others interviewed by phone reported no adverse effects. Twenty-one (21) patients were not available for evaluation."

Notably, there were 218 reports of TVT mesh (tape) erosion in the MAUDE database through 2008 (date of 11.5-year study follow-up discussed above), about which Ethicon knew or should have known. Twiss and Raz[429] in this same time period reviewed the literature to summarize rates, etiology, and management of the most common complications encountered with synthetic mid-urethral slings. Postoperative vaginal erosions were noted to be a problem with synthetic slings, with large case series of TVT procedures showing vaginal erosions occurring in 0.2% to 1.8% of cases. Urethral erosions were noted but occurrence rate was not provided. As noted above, a 2004 review by Bhargava and Chapple of the literature dated 1995 to 2004 on the complications of synthetic suburethral slings, including TVT, reported sling erosion to be one of the most frequently and potentially serious complications with the use of synthetic slings. While the introduction of newer sling materials such as TVT (and SPARC) appeared to have reduced the incidence of erosion, studies were noted to report incidences between 0.3% and 4.4%.[430] While the rate of erosions may be low, presentation and management of erosion may be associated with a significant risk of morbidity. For example, Deng et al.[431] presented their experience as a tertiary referral center (UCLA) for major complications of mid-urethral slings. Between June 2001 and August 2005, 26 patients' histories were reviewed and details of the presentation and management of complications were reported. Of the 26 patients, 12 had TVT devices implanted. Findings included mesh in the urethra, bladder, urethra and bladder, or mesh in the urethra with urethrovaginal fistula. Treatment required excision and reconstruction or, in the cases of mesh in the urethra plus urethrovaginal fistula, excision and Martius flap were performed.

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[426] ETH.MESH.02237103: Marketing piece titled "Dependability - GYNECARE TVT™ Family of Products Tension-free Support for Incontinence," 2010.

[427] It should also be noted that in the Nilsson publication of the 11.5 year follow up, Professor Nilsson specifically states that there are no conflicts, when that obviously was not the case. Nilsson et al. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J 2008;19:1043-1047 at 1046

[428] ETH.MESH.00355003 at 003, 005: Nilsson et al. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J 2008;19:1043-1047.

[429] Twiss C and Raz S. Complications of Synthetic mid-Urethral Slings. Issues in Incontinence, Laborie.com, Spring/Summer 2008.

[430] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.

[431] Deng et al. Presentation and management of major complications of midurethral slings: Are complications under-reported? Neurourology Urodynamics 2007;26:46-52.

Additionally, Deng et al. reviewed both the literature on midurethral slings that included complications in the analysis and also the MAUDE database. These authors noted the discrepancy in reporting of major complications between the literature and the MAUDE database and point out that a true denominator is unknown and, thus, an incidence for major or minor complications cannot be calculated, nor can quantitative comparisons be made between the published literature and the MAUDE database. Moreover, these authors state that practitioners of SUI surgery tend to rely on the published literature as representative data, and therefore may not be aware that sling procedures may be associated with a significant risk of morbidity and mortality, as it may be that the more serious complications tend to be in the MAUDE database.[432] Misleading information such as presented in the marketing pieces discussed herein only further limit the physician's awareness of the potential risks associated with the TVT device.

OPINION #3: TVT System Misbranded as a Result of False or Misleading Labeling

The definition of "false or misleading" is not confined to meaning untrue, fraudulent, or deceptive. Labeling can be deemed by FDA to be misleading and in violation of FDA requirements if it proves deceptive to the customer by creating or leading to a false impression in the mind of the reader. Failure to inform the consumer of facts relevant to statements actually made may cause a "false impression," such that labeling that remains silent concerning certain consequences may be as deceptive as labeling that contains extravagant claims.[433] Labeling that fails to reveal material facts and consequences that may result from product use is considered misleading. Thus, product labeling that fails to include risk information and warnings important to safe use is considered false and misleading.

Ethicon utilized promotional labeling that was false and misleading and failed to reveal material facts. This constituted misbranding. The introduction or delivery for introduction into interstate commerce of any device that is misbranded is a violation of Section 301(a) of the FDCA.[434] Thus, Ethicon deviated from the standard of care required of a medical device manufacturer by the multiple ways in which the TVT device was misbranded, including professional and patient labeling and also promotional labeling that was false and misleading in its representations and/or failed to include known or knowable safety information.

IX. FDA ACTIONS: SERIOUS COMPLICATIONS ASSOCIATED WITH TRANSVAGINAL PLACEMENT OF SURGICAL MESH IN REPAIR OF STRESS URINARY INCONTINENCE

A. 2008 FDA Public Health Notification

By 2008, FDA was aware of potential safety issues with urogynecologic surgical mesh products because of information received through multiple sources. These sources included (1) postmarket

[432] *Id.*
[433] Medical Devices: Labeling Requirements – Misbranding (Available at www.fda.gov).
[434] 21 U.S.C. § 331(a).

surveillance of the MAUDE database for medical device reports (MDRs), (2) concerns raised by the clinical community and citizens, and (3) the published literature.

A search of the MAUDE database in 2008 showed that more than 1000 MDRs had been received from 2005-2007. These were reports of complications from nine surgical mesh manufacturers of surgical mesh devices used to repair pelvic organ prolapse (POP) and stress urinary incontinence (SUI).

As a result of these findings, FDA issued a *Public Health Notification* (PHN) in October 2008 informing clinicians and their patients of these findings, with recommendations on how to mitigate risks and how to counsel patients, titled **"Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence."**[435]

According to the 2008 PHN:

"The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia."

B. 2011 FDA Safety Communication

In January 2011, the FDA completed another search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2,874 MDRs for urogynecologic surgical mesh; of these, 1,371 were associated with SUI repairs.[436]

On July 13, 2011, FDA issued a *Safety Communication* to update the 2008 PHN.[437] Although directed to health care providers who treat either POP and/or SUI, and patients contemplating or who have received either type of mesh, the Safety Update was primarily concerned with POP repair. However, according to the *Safety Communication*, "[i]n order to better understand the use of surgical mesh for POP and SUI, the FDA conducted a systematic review of the published scientific literature from 1996 – 2011 to evaluate its safety and effectiveness. The review showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair. The FDA continues to evaluate the literature for SUI surgeries using surgical mesh and will report about that usage at a later date."[438]

[435] FDA *Public Health Notification*: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, Issued October 20, 2008.
[436] FDA *Safety Communication*: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse, Issued July 13, 2011.
[437] *Id.*
[438] *Id.*

C. 2011 Meeting of Obstetrics and Gynecology Devices Advisory Committee and January 4, 2012, Update

In September, 2011, as a result of the above-discussed findings, FDA convened a meeting of the Obstetrics and Gynecology Devices Advisory Committee to discuss "Surgical Mesh For Treatment Of Women With Pelvic Organ Prolapse And Stress Urinary Incontinence." As a background document for this meeting, FDA published an Executive Summary summarizing outcome efficacy and safety data obtained from published literature and the MAUDE safety database.[439] From 1992-2010, the FDA cleared 83 510(k)s for surgical mesh with an SUI indication, 63 with a POP indication, and 22 with both. Meshes were categorized according to whether the indications for use included "reconstruction of the pelvic floor" or "pubourethral support." Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies. The FDA premarket notification review process did not request original clinical studies to support 510(k)-clearance. However, in their Executive Summary, FDA states that "A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices."[440]

The types of adverse events reported to the FDA's MAUDE database during 2008 to 2010 for surgical meshes to treat SUI were death (n=3), injury (n=1131), malfunction (n=236), and "other" (n=1). Of the three deaths reported, two were related to the mesh placement procedure (two bowel perforations), but unrelated to the mesh itself. One death was related to complications from removal of eroded mesh. Types of non-fatal adverse events are presented in Table IX.1. below.

Table IX.1.: Number and Percent of Adverse Event for SUI Reported to MAUDE (2008-2010)

Adverse Event	# of Reports[1]	Percent[2]
Pain	479	34.9
Erosion	436	31.8
Infection	260	18.9
Urinary Problems	220	16.0
Organ Perforation	110	8.3
Recurrence, Incontinence	103	7.5
Bleeding	103	7.5
Dyspareunia	73	5.3
Neuromuscular Problems	50	3.6
Vaginal Scarring	22	1.6

[1] The total number of reports is greater than the number of MDRs because most MDRs reported more than one adverse event.
[2] Total number of reports divided by 1371 (total number of MDRs received)

[439] FDA Executive Summary. Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. Obstetrics & Gynecology Devices Advisory Committee Meeting, September 8-9, 2011.
[440] *Id.*

The most frequent required interventions were additional surgical procedure (394), partial or complete mesh removal (162), and hospitalization (58). Other less severe interventions included application of topical estrogen cream, a course of antibiotics or trimming of the exposed mesh.

The FDA also undertook a review of the published literature for safety data associated with SUI slings. They included 187 studies in their review, of which 102 were observational studies and 85 were randomized controlled trials. The most commonly studied procedure using mesh for SUI repair was the TVT procedure, followed by the TOT procedure. Most of the available information was heavily weighted from the perioperative period (intraoperative to 48 hours postoperative) to one year postoperative. Few studies had follow-up longer than three years. The most commonly reported adverse events in the literature associated with surgical mesh for SUI repair included erosion, dyspareunia, infection, pain, urinary problems (including de novo SUI, urgency, frequency and overactive bladder), and re-surgery. Between 9% and 17% of patients who had SUI treated with surgical mesh reported urinary problems from 6 months postoperatively to 60 months postoperatively. It also appeared that with time there were increases in the proportion of women reporting urinary problems, re-surgery (range 2.5% at 6 months postoperatively to 6.2% at 12 months postoperatively), and any infection (5.1% perioperatively to 27.6% at 60 months postoperatively). The trend in urinary problems appeared to be largely driven by TVT procedures, compared to TOT procedures. The latter procedure demonstrated consistent rates (roughly 10%) of urinary problems across study follow-up periods.

The trend observed with urinary problems was similar with infection rates. Women who underwent TOT procedures had lower weighted rates of infection than women who had TVT procedures. Furthermore, it was observed that among TVT and TVT-O procedures, infection rates appeared to increase over time, while infection rates among TOT procedures decreased from 10% during the perioperative period to 0.4% at 24 months postoperatively.

There was no apparent trend in erosion rates, which ranged from 0.25% to 4% from 6 months postoperatively to 60 months postoperatively. Weighted rates of reported pelvic or vaginal pain ranged from 22.2% at 60 months to 1.6% at 36 months but more consistently averaged at about 5%. Neuromuscular adverse events were reported at a rate of 1% or less over the follow-up measurement periods. Dyspareunia rates ranged from a high of 13.7% at 60 months to 0.64% at 12 months.

The most common perioperative complications associated with sling procedures were organ perforation (including bladder, urethral, vaginal, and bowel perforation), hemorrhage, and hematomas. The TVT procedure had a lower rate of perforation (4.4%) than the SPARC procedure (10.1%) or pubovaginal slings (8%), and a higher rate than the TOT procedure (1.7%). Definitions of hemorrhage and hematoma were disparate or absent across the literature; therefore no clinically significant conclusions could be drawn.

Other risks of minimally invasive synthetic slings include perioperative complications such as bladder perforation and groin pain. FDA also concluded that there is potential for serious complications with SUI mesh. They expressed concerned that safety outcomes may not have been comprehensively evaluated by RCTs to date and noted that the safety of SUI repair with mesh needs to be further considered in evaluating the overall risk to benefit profile of these products.

However, they stated that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (e.g., new polymer or coating) that could affect device performance. This is despite the relatively short duration of follow-up (2 years) for most of the studies.

In a January 2012 Update, FDA advised that it continues to assess the safety and effectiveness of urogynecologic surgical mesh devices through a number of sources, including the published literature, epidemiological research on safety and effectiveness of surgical mesh, collaborations with professional societies and other stakeholders to fully understand the postmarket performance of urogynecologic surgical mesh devices and the occurrence of signs and symptoms associated with specific adverse events, and collecting and reviewing all available information about currently marketed urogynecologic surgical mesh devices.[441]

X. POSTMARKET VIGILANCE ISSUES AND MISBRANDING

A. Significance of Postmarket Vigilance

"Postmarket vigilance" means all scientific and data collection activities related to the detection, evaluation, and understanding of adverse events. The primary objective of postmarket vigilance is to identify and evaluate any potential safety signal. The term "signal" refers to a potential safety issue or concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Importantly, in order for an event to be considered a signal, a causal relationship between the device and the event does not need to have been established.

Postmarket vigilance is critical to ensuring that informed and timely decisions are made concerning medical device safety and, thereby, risk to patients is minimized.[442] A manufacturer's postmarket vigilance program can only be effective if all company employees or representatives who learn about complaints, including both adverse events and malfunctions, report them to the individual(s) designated within the company, according to established procedures, for evaluation, investigation, and reporting to FDA as required. Further, those individuals with responsibility for receipt, evaluation, investigation, and reporting of adverse events to FDA, in accordance with applicable requirements (as discussed in Section II.G.), must perform their responsibilities with objectivity, due diligence, and with the ultimate goal of assuring that all safety issues that meet the regulatory reporting requirements are both assessed internally and also submitted to FDA in a timely manner, and that corrective actions are implemented as necessary to protect the public health.

Safety signals can arise from multiple sources: postmarket data for a company's own product, including complaint reports from consumers made directly to the company, reports to FDA that are captured on the FDA's adverse event databases, and information from postmarketing clinical studies; scientific and medical literature; and events associated with other similar products. After a signal is identified, it should be further investigated to determine whether it represents a potential

[441] FDA UPDATE 01/04/2012: Urogynecologic Surgical Mesh Implants.
[442] Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. March 2005, U.S. FDA, CDER/CBER.

safety risk and whether other action should be taken. Such investigation may or may not lead to the conclusion that the device caused the event. FDA advises that a manufacturer should initially evaluate a signal through a careful review of individual case reports and a search for any additional cases. When one or more cases indicate a safety signal that needs further investigation, FDA recommends summarizing the available clinical information in order to characterize the potential safety risk and identify risk factors, if possible.

This section of my Report will discuss Ethicon's actions and inactions according to the MDR regulations and postmarket vigilance activities.

B. Medical Device Reporting/MAUDE Database

As discussed previously in this Report, medical device manufacturers are required to report to the FDA all device-related deaths, serious injuries, and certain malfunctions, in accordance with the Medical Device Reporting (MDR) regulations.[443] Medical Device Reporting provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events in order to detect and correct safety problems in a timely manner. Achieving this purpose is dependent on the compliance and cooperation of the medical device manufacturer to perform its surveillance, investigatory, reporting and follow-up responsibilities, as described above.

MDR reports submitted to FDA are entered into the Manufacturer and User Facility Device Experience (MAUDE) database, which contains reports of adverse events involving medical devices and is accessible via the FDA website. The MAUDE database includes not only MDRs from manufacturers but also MDR reports from user facilities and voluntary reports from such sources as healthcare practitioners, patients, and consumers (e.g., attorneys). The sooner the FDA learns about a problem, the sooner the Agency can take action to evaluate actual or potential risk and ensure that any necessary corrective action is initiated to protect patient safety. Sometimes a single report can initiate this action.[444]

To evaluate the serious adverse event information of particular relevance to the TVT System and known or knowable to Ethicon based on the MAUDE database, an independent search/review of the MAUDE database for Medical Device Reports (MDRs) was undertaken using the methodology described in Exhibit 1. Summary results of that review are presented below. Tabulations providing additional detail and supporting the summary results also are provided in Exhibit 1.

C. Summary of TVT Medical Device Reports

A total of 1,173 Medical Device Reports for the TVT device were located in the MAUDE database (includes 372 TVT reports for which the product catalog number was not available). Of the 1,173 reports, 1,093 were manufacturer reports, 74 were voluntary reports, and six were user facility reports. The reason for surgical implantation of the mesh was not specified for most of the reports (1,018 reports) or stated to be SUI (124 reports) and/or POP (56 reports).

[443] 21 CFR Part 803.

[444] Improving Patient Care by Reporting Problems with Medical Devices. *A MedWatch Continuing Education Article*. Uniformed Services University of the Health Sciences and FDA. September 1997.

It is important to note that, for many patients, more than one adverse event was reported. Also, for this analysis, not every occurrence of a named sign, symptom, or illness was counted; instead, the specific signs, symptoms, and illnesses reported were counted. For example, any number of urinary tract infections (UTIs) described for a particular report was counted only once.

1. Most Commonly Reported Adverse Events

The most commonly reported adverse events, i.e., defined as those occurring in 2% or more of MDR reports, included those listed below in Table X.1. The total number of most commonly reported adverse events and also the percentage of total MDR reports in which such events were reported are shown. Of note, adverse events related to the urinary system are reported collectively as urinary problems in Table X.1. The multiple adverse events represented by "urinary problems" are specified in Section 1.B. of Exhibit 1 and are tabulated by year of report date in Section 2 of Exhibit 1. Similarly, as regards mesh erosion and organ perforation, the organs involved are delineated in Section 1.B. of Exhibit 1 and are tabulated by year of report date in Section 2 of Exhibit 1. As regards the other most commonly reported events, where different reporting terms were used for like events, these were combined as shown in Section 1.B. of Exhibit 1 for the purpose of this analysis and also are tabulated by year of report date in Section 2 of Exhibit 1.

Table X.1. Most Commonly Reported Adverse Events in MAUDE Database: 1999-2010

Event	n	% of total MDRs (1,173)
Urinary Problems	405	34.5%
Erosion	377	32.1%
Pain	291	24.8%
Bleeding	151	12.9%
Sexual Dysfunction	117	10.0%
Organ Perforation	103	8.8%
Infection	82	7.0%
Unspecified Illness/Issues/Injuries	67	5.7%
Discharge	54	4.6%
Wound Healing Problems	45	3.8%
Neurologic Compromise or Damage	35	3.0%
Scarring	34	2.9%

Other adverse events reported are listed in Section 1.B. of Exhibit 1. Patient outcome information reported also is shown in Section 1.B. of Exhibit 1. Some reports do not state a patient outcome.

It is important to note that there were 15 deaths reported associated with TVT implantation. Number of deaths by year reported are indicated following: 1998 (one); 1999 (two); 2000 (one); 2001 (one); 2002 (two); 2003 (three); 2004 (one); 2005 (two); 2008 (one); 2010 (one). Among the causes of death or information available regarding these deaths were the following:

- Bladder mesh, sepsis, and anemia listed on death certificate as cause of death, anterior wall defect;

- During follow-up surgery, patient died when she went into septic shock;
- Patient died in postoperative course from major septic state;
- Expired due to bowel perforation;
- Bowel perforation noted in follow-up surgery, patient died post-op;
- Bowel perforation and abscess noted after surgery;
- Cecal perforation noted after initial surgery and patient developed disseminated intravascular coagulopathy;
- Lost consciousness and expired after surgery;
- Died during initial surgery;
- Patient required resuscitation twice and third resuscitative effort was unsuccessful and patient expired;
- Hematoma evacuated, patient had seizure-like event two days later and died due to pulmonary embolism arising from occult deep vein thrombosis;
- Venous bleeding occurred, vasovagal attack and cardiac arrest.

2. ***Comparison of MDR Reports Located for TVT vs. FDA's MAUDE Search Across SUI Mesh Products of Multiple Manufacturers: 2008-2010***

Table X.2. below shows the number of MDR reports for each adverse event that FDA identified in its Executive Summary of safety data obtained from its search of the MAUDE safety database for the time period 2008 to 2010, which included multiple manufacturers of surgical mesh for the treatment of SUI;[445] also shown are the number of MDR reports identified for TVT for each adverse event in the independent search/review of the MAUDE database for MDR reports using the methodology described in Exhibit 1. Based on this information, for each adverse event, the percentage of events across all manufacturers attributable to TVT is shown.

It is particularly notable that TVT accounts for 82.2% of dyspareunia reports, yet this never appeared in the TVT IFU/professional labeling. Except for organ perforation and infection, for which TVT accounted for 10% and 16.5% of these reported events, respectively, TVT accounted for a third or more of each adverse event identified by FDA as a potential safety concern with the use of surgical mesh to treat stress urinary incontinence. As discussed below in Section X.D., Ethicon underreported some of these adverse events for TVT, e.g., erosions and organ perforation.

[445] FDA Executive Summary. Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. Obstetrics & Gynecology Devices Advisory Committee Meeting, September 8-9, 2011.

Table X.2. TVT MDRs versus "All" SUI Mesh Product MDRs: 2008-2010

Adverse Event	All Mesh Product Reports[1]		Ethicon TVT Reports		% TVT of All SUI Mesh Reports
	n	%[2]	n	%[3]	
Pain	479	34.9	158	47.3	33
Erosion	436	31.8	195	58.4	44.7
Infection	260	18.9	43	12.9	16.5
Urinary Problems	220	16.0	110	32.9	50.0
Organ Perforation	110	8.3	11	3.3	10.0
Recurrence, Incontinence	103	7.5	40	12.0	38.8
Bleeding	103	7.5	37	11.1	35.9
Dyspareunia	73	5.3	60	18.0	82.2
Neuromuscular Problems	50	3.6	32[4]	9.6	Not applicable[5]
Vaginal Scarring	22	1.6	31[6]	9.3	Not applicable[5]

[1] The total number of reports is greater than the number of MDRs because most MDRs reported more than one adverse event.
[2] Total number of reports divided by 1371 (total number of MDRs received)
[3] Total number of reports divided by 334 (total number of Ethicon TVT reports found through FDA MAUDE database search)
[4] Neuromuscular problem as a specific term was not identified in the TVT MDR reports; the 32 reports shown were for neurologic compromise (26) and nerve damage (6).
[5] Because terms in the TVT MDR reports did not specify location of scarring or further define nerve damage/compromise, a percentage of all mesh product reports is not given.
[6] Includes 29 reports of "scar tissue" and two reports of "scarring"; location of scar tissue/scarring was not specified.

3. Reported Interventions

As regards follow-up surgery, 348 (30.0%) of the MDRs reported that the patient had undergone one follow-up surgery, 177 (15.1%) reported that the patient had undergone two or more follow-up surgeries, and 94 (8.0%) reported that the patient would undergo surgery as a result of the reported adverse events for a total of 619 (52.8%) patients who required surgery or for whom surgery was planned.

Interventions other than surgery and planned surgery are listed in Section 1.D. of Exhibit 1, along with the number of patients for which each intervention type was reported.

4. Initial Reports and Follow-Up Reports

The majority of reports located by the MAUDE DB search were labeled "Initial." While the FDA received most initial reports within 30 days of manufacturer receipt of the report, as required, there were 88 reports with a somewhat longer reporting interval. Sixty-seven (67) reports were reported between 31 and 44 days, six (6) were reported between 45 and 60 days, eight (8) were reported between 61 and 90 days, and seven (7) were reported between 91 and 212 days. A total of 101 reports did not have an entry for "date manufacturer received."

D. TVT Issue Reports, including Investigation Records

An Issue Report is the form Ethicon uses to record complaints, investigation of complaints, and the determination of reportability to regulatory authorities. There were 862 TVT Issue Reports received and reviewed for this Report (date range: 1999-2012). Of these, Ethicon submitted 603 (70%) as MedWatch (MDR) reports to FDA, and 258 (29.9%) were determined by Ethicon to be "not reportable." One was undetermined. Review of the Issue Reports that Ethicon determined to be "not reportable" showed that a number met the requirements for MDR reporting and should have been submitted to FDA in my professional opinion. The basis for this opinion and representative examples are discussed below.

Medical Device Reporting requires that if a manufacturer becomes aware of information that reasonably suggests that its device may have caused or contributed to a serious injury or malfunctioned and the device would be likely to cause or contribute to death or serious injury if the malfunction were to recur, it must report that information to FDA.[446] "Serious injury" includes injury that "results in permanent impairment of a body function or permanent damage to a body structure," or injury that "[n]ecessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure." "Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage."[447] Definitions of other key terms such as "becomes aware," "reasonably suggests," and "caused or contributed" were provided previously in Section II.G.2.1. of this Report. Importantly, a serious injury is not required actually to have occurred for the event to be considered reportable under this definition.[448]

1. MDR-Reportable Adverse Events Determined by Ethicon to be Not Reportable

Provided in Exhibit 3 in tabular format are 29 examples of adverse events that Ethicon determined were not MDR-reportable but should have been reported to FDA as MDRs in my professional opinion. These include 15 reports of erosion/extrusion, five of which resulted in dyspareunia or pain/discomfort to the sexual partner and four of which noted incontinence, including de novo urge incontinence which was specified for one patient and also bladder perforation in one patient. Incontinence was reported in an additional eight (8) reports: incontinence and also hematoma (one report); urge incontinence/urgency and urgency leak (four reports); recurrent SUI (two reports); and worsening of urgency incontinence (one report). There were three additional reports of bladder perforation, one report of blood vessel perforation with hematoma, an additional report of vaginal pain and dyspareunia, and one report of possible TVT allergy.

Of these 29 examples, seven representative complaints involving mesh erosion/extrusion and organ perforation, which are among the adverse events most commonly reported in the MAUDE database for SUI mesh products across multiple manufacturers (based on FDA's search, date range: 2008-2010), are discussed below. In particular, the reasons in my professional opinion that these events were MDR-reportable are presented.

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[446] 21 CFR § 803.20(b)
[447] 21 CFR § 803.3.
[448] Mathewson NW. Complaint Handling and Medical Device Reporting. In *Medical Device Regulation & Compliance*. Eds. Terman SD and O'Flaherty NF. FDLI 2010.

1.1 Mesh Erosions/Extrusions Ethicon Determined Were Not MDR-Reportable

Erosions and extrusions are noted to be potential adverse reactions in the TVT product labeling, i.e., the IFU. As shown above in the discussion of TVT MDR reports, there were 377 MDR reports of mesh erosion, including 151 reports of vaginal mesh erosion and 138 reports of unspecified erosion, during the 1999-2010 time period; of these, 328 total reports of mesh erosion, including 120 reports specified as vaginal erosion, were reported to FDA by Ethicon. It is noteworthy that vaginal erosions requiring a procedure for correction may be treated in the physician's office or in the hospital, but intervention in both cases is considered a surgical revision.[449]

A manufacturer must evaluate each adverse event or malfunction reported and make a good faith determination consistent with the regulations and industry standard of practice, including applying the same logic every time a complaint is evaluated. This is critical for the manufacturer to be able to analyze and trend complaint data to identify any product problem that requires corrective and preventive action. The examples discussed below demonstrate that Ethicon did not consistently submit MDR reports for mesh erosion and, consequently, underreported to FDA the occurrences of mesh erosion following TVT implantation about which it was aware, in violation of the industry standard of care.

a) On January 30, 2002, Ethicon was notified of a patient who presented with minimal asymptomatic vaginal extrusion (Tracking number 30001906).[450] No medical intervention was performed at the time but it was noted that topical estrogen would be used or the mesh would be trimmed if the patient became symptomatic. "The physician felt that the extrusion was probably the result of vaginal atrophy along with passgage [sic] of the needle too close to the vaginal mucosa"; thus the physician noted possible user error. This event was not reported as an MDR on the basis of Ethicon's medical review which concluded that "the patient *will not require* any medical or surgical intervention to correct the extrusion or to otherwise preclude serious injury or permanent damage with regards to the structure or function of the vaginal area." (Emphasis added.) Notably, it was speculation in my professional opinion for the medical reviewer to conclude that the erosion would not worsen and/or require treatment, and I reviewed no evidence of follow up by Ethicon to determine outcome of the erosion. The status was indicated as closed within approximately two months of the alert date.

   As discussed above, a serious injury is not required actually to have occurred for the event to be considered reportable.[451] Additionally, regardless if user error contributed to the occurrence of erosion, the event should be reported if it meets the criteria for MDR reporting. The regulation does not exempt events caused by user error from reporting requirements. In fact, FDA has stated that "reports of adverse events that result from user error may alert FDA to the need for improved labeling to prevent future injuries."[452] It is significant that approximately 40% of Medical Device Reporting (MDR) filings involve

[449] Dr. Piet Hinoul deposition, June 27, 2013, 487:9-20.
[450] ETH.MESH.02622556-559: Issue Report (Tracking Number: 30001906).
[451] Mathewson NW. Complaint Handling and Medical Device Reporting. In *Medical Device Regulation & Compliance*. Eds. Terman SD and O'Flaherty NF. FDLI 2010.
[452] 60 *Fed. Reg*. 63583.

user error. One of the problem areas is labeling. In addition to the cases where there is a primary association between labeling and MDR reports, labeling can also be an "underlying" or secondary cause of misuse that leads to MDR reports.

Although the rationale given for not reporting this event states that "[t]his event is not indicative of any product malfunction," the device did not perform as intended. FDA indicates that a malfunction is considered reportable if the device is a long-term implant or if a malfunction of the same type has actually caused or contributed to a serious injury in past, both of which apply to the TVT device. Furthermore, if Ethicon considers vaginal atrophy and passage of the needle too close to the vaginal mucosa to be factors that increase the risk of vaginal erosion, then Ethicon had the obligation to include this information in the Warnings and Precautions section of the labeling.

b) Ethicon became aware on August 21, 2002, that a patient approximately six weeks after TVT implantation presented with a loop of the mesh (tape) approximately 3 cm long in the vagina (Tracking number 30002788).[453] Medical intervention to resolve the erosion was to trim the tape. The surgeon attributed the extrusion to an episode of coughing during the postoperative period, and the Ethicon Medical Director agreed. However, the issue report documents that the injury required medical or surgical intervention and that intervention was required to prevent permanent impairment of a body function or permanent damage to a body structure, which by definition makes this an MDR-reportable event. Considering that erosion/extrusion is a labeled adverse reaction, it is not only speculation but also disingenuous to attribute the tape extrusion to coughing. If the Medical Director believed that coughing postoperatively could result in tape extrusion, this information should have been included in the Warnings and Precautions section of the product labeling.

c) On September 20, 2002, an Ethicon Medical Director was contacted by a urologist who reported a 51-year-old woman with vaginal mesh extrusion and dyspareunia two months after TVT implantation (Tracking number 30002949).[454] Medical intervention was reported: cutting of the exposed portion of the tape vaginally. The physician theorized that corticosteroids may have been responsible for thinning of the vaginal wall and tape extrusion. On that basis, Ethicon decided not to report this event as an MDR. Similar to the notation above in paragraphs "a" regarding the report of mesh extrusion as probably related to vaginal atrophy, if Ethicon considers corticosteroid usage to be a risk factor for vaginal extrusion, then the company had the obligation to include this information in the Warnings and Precaution section of the labeling. Notably, the issue report documents that the injury required medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure, which by definition makes this an MDR-reportable event. Disingenuously, the issue report also documented that a person qualified to make a medical judgment concluded that the malfunction would not be the cause or contribute to a death or serious injury if it were to recur. Yet through 2001, Ethicon submitted at least 10 reports of vaginal erosion to FDA as a serious injury, with an additional at least 34 such reports submitted to FDA as MDR reports in 2002. Through 2001, Ethicon submitted nine (9) reports of dyspareunia to FDA as a serious injury, with an

[453] ETH.MESH.02623207-210: Issue Report (Tracking Number: 30002788).
[454] ETH.MESH.02623462-465: Issue Report (Tracking Number: 30002949).

additional 25 such reports submitted to FDA as MDR reports in 2002. By Ethicon's own prior actions, vaginal erosion and dyspareunia are MDR-reportable events.

d) On May 18, 2005, a sales representative reported a customer complaint of multiple adverse events following a vaginal hysterectomy and TVT procedure on May 19, 2004 (Tracking number 30005380).[455] Specifically, since that time, the patient had experienced a series of ongoing post-operative problems: De novo urge incontinence within the first two weeks postoperative, for which Detrol medication was initiated; multiple bladder infections within the past year with no history of bladder infections prior to the procedure; two vaginal tape erosions, both of which required procedures to cut out the tape and, as specified for the second procedure, re-sew the vaginal mucosa on top. Dr. C. Owens reviewed this complaint and provided her assessment that "[u]rge incontinence is sometimes unmasked or a transient known occurrence after TVT placement. When it is transient it is usually self limiting. This is not unique to the TVT device as any sling procedure can have this occur after." It is notable that her discussion is in regard to *transient* urge incontinence, yet this problem had been ongoing for one year when reported. Dr. Owens's further assessment stated that "[m]esh exposure is influenced by many factors including an inadequately estrogenized vaginal mucosa, trauma, improper closure and other things, but not the direct fault of the mesh as this can occur with any permanent implant." As discussed above regarding other events of erosion or extrusion that were not submitted as MDR reports, if Ethicon considered inadequately estrogenized vaginal mucosa, trauma, and improper closure to be risk factors for erosion, the company had the obligation to include these in the Warnings and Precautions section of the labeling. Finally, the rationale provided for not reporting this complaint was "that there was no device malfunction or serious injury [that] occurred. Persistent urinary stress incontinence following a sling procedure with TVT is likely the result of sub optimal placement of the device and is not likely due to the failure of the device itself. The patient would have the same clinical presentation as before the procedure and this condition is not considered life threatening or serious to the patient." It is noteworthy that this rationale focuses on SUI, yet Dr. Owens specifically commented that the patient's ongoing incontinence is not SUI according to the urodynamics noted in the complaint. Further, the rationale ignores that the device failed to perform as intended, notably, that the patient had two erosions that required medical or surgical intervention; additionally, the patient experienced multiple bladder infections. It is disingenuous to conclude that no serious injury occurred, when by end 2004, Ethicon, to the contrary, had reported at least 80 cases of vaginal erosion to FDA as serious injuries and an additional 57 cases of unspecified erosion or erosion into other organs, for a total of 137 reports of mesh erosion submitted to FDA as serious injuries. Moreover, Ethicon had reported 40 complaints of incontinence to FDA as serious injuries and 20 complaints of urinary tract infections to FDA as serious injuries by end 2004. As regards the speculation that persistent SUI is likely the result of sub-optimal placement of the TVT, even if this were true, the regulation does not exempt events caused by user error from reporting requirements, as previously discussed.

e) On June 20, 2005, Ethicon received a report of a gynecologist stating that s/he has had four or five erosions since the tape was changed to blue, yet had no erosions previously with the

[455] ETH.MESH.02627651-655: Issue Report (Tracking Number: 30005380).

undyed tape during an 18-month period (Tracking number 30005489).[456] Physician stated belief that the dying procedure had affected the property of the tape, as it is less soft, pliable and flexible. Medical Director Dr. C. Owens provided the medical opinion that the blue pigment would not alter the physical characteristics and be responsible for the mesh exposures, but exposures are influenced by such factors as "inadequately estrogenized vaginal mucosa, trauma, improper closure and other things, but not the direct fault of the mesh as this can occur with any permanent implant." Further rationale for not reporting these events was "that neither serious [injury] nor device malfunction which could lead to a serious injury have occurred. Event reported is a customer preference issue. It does not affect the efficacy of the product or present a risk for serious injury to the patient." As discussed above regarding other events of erosion or extrusion that were not submitted as MDR reports, if Ethicon considered inadequately estrogenized vaginal mucosa, trauma, and improper closure to be risk factors for erosion, the company had the obligation to include these in the Warnings and Precautions section of the labeling. Further, as also discussed above, it is disingenuous to conclude that neither serious injury nor malfunction that could lead to serious injury had occurred, when by end 2004, Ethicon had reported at least 80 cases of vaginal erosion to FDA as serious injuries and an additional 57 cases of unspecified erosion or erosion into other organs, for a total of 137 reports of mesh erosion submitted to FDA as serious injuries. Significantly, I found no evidence to indicate that any effort was made to investigate the multiple cases of erosion reported in this complaint in order to learn and report, as necessary, patient outcomes.

1.2 Organ Perforations Ethicon Determined Were Not MDR-Reportable

Punctures or lacerations of vessels, nerves, bladder or bowel during needle passage, possibly requiring surgical repair, are noted to be potential adverse reactions in the TVT product labeling. As shown above in Table X.1., there were 103 MDR reports of organ perforation submitted during the 1999-2010 time period, of which 98 were submitted by Ethicon. The examples below of complaints involving organ perforation demonstrate that Ethicon was inconsistent in its determination of MDR-reportability of such events and that Ethicon underreported to FDA occurrences of organ perforation following TVT implantation, just as it underreported mesh erosion and extrusion, in violation of the industry standard of care.

a) Ethicon received a call on September 24, 2004, from a sales representative with a physician complaint regarding TVT. Ethicon WCQ appropriately followed up to obtain more information and learned that the surgeon had performed a TVT procedure on August 10, 2004, and inadvertently punctured the patient's bladder during the procedure (Tracking number 30004870).[457] The first device was removed and a second one was placed. Two days later the patient complained of urinary retention and was managed with Ditropan. A cystoscope was performed (apparently on September 30, 2004) and revealed a vaginal mesh erosion and "something pressing on the bladder," which was causing frequency and incontinence. It was also reported that the cystoscope identified fragments of mesh in the bladder from the original inadvertent bladder perforation.

[456] ETH.MESH.02627743-747: Issue Report (Tracking Number: 30005489).
[457] ETH.MESH.02627146-150: Issue Report (Tracking Number: 30004870).

Ethicon Medical Director Dr. Owens reviewed the complaint and followed up appropriately to obtain more information. In addition to the above information, Dr. Owens learned that the patient required a Foley catheter for several days and continued to have some urinary retention after removal of the Foley catheter, such that she had to move her body into certain positions in order to void. Shortly after catheter removal, she developed urge and frequency and a cystoscopy was performed by a urologist, who observed "pieces of the TVT in the bladder and a suburethral erosion in the vaginal mucosa with a finger like 'something', maybe a hematoma, compressing down on the left side of the bladder." Removal of the TVT device was planned within approximately one week. Patient had urgency and incontinence. Dr. Owens noted that the individual with whom she spoke (name redacted) felt the pieces in the bladder were not erosions but were left behind when she removed the TVT device after perforating the bladder. Further, Dr. Owens noted that the "bladder entry was technique-related and also related to the fact that the patient had a history of previous surgery which may have also contributed. The vaginal erosion of TVT tape may be the result of many factors including an inadequately estrogenized vaginal mucosa, trauma, improper closure and other things, but not the direct fault of the device as this can occur with any permanent implant."

Rationale for not reporting stated that "no serious injury or device malfunction occurred in this event. No medical intervention was provided for the bladder perforation and per the Medical Director the etiology of the bladder entry was technique related and also related to the fact that the patient had a history of previous surgery that may have also contributed."

Similar to the above discussions regarding examples of mesh erosion or extrusion that were not reported as MDRs but should have been in my professional opinion, it is disingenuous to conclude this patient had no serious injury or device malfunction and no medical intervention. To the contrary, the device did not perform as intended. The device eroded into the vagina and the patient was incontinent with urgency after the TVT implantation. The patient received medication to manage urinary retention postoperatively and subsequently underwent cystoscopy. A possible hematoma was observed. Surgery to remove the mesh was planned in the near term, yet I found no evidence of follow-up to determine outcome post removal of the device or to determine if there were any deleterious effects of the mesh pieces remaining in the bladder. Instead, this complaint was closed out within 18 days after Ethicon became aware of this complaint. As regards the Medical Director's conclusion that the bladder perforation was technique-related, user error does not justify the failure to report this event. Specifically, the regulation does not exempt events caused by user error from reporting requirements. As noted previously, FDA has stated that "reports of adverse events that result from user error may alert FDA to the need for improved labeling to prevent future injuries."[458] Further, if Ethicon considers that a patient's prior surgical history elevates the risk for bladder perforation, then Ethicon had the obligation to include this information in the Warnings and Precaution section of the labeling.

b) Ethicon Medical Director became aware on March 24, 2005, of a TVT procedure on that day in which cystoscopy showed mesh in the bladder, at which point the decision was made

[458] 60 *Fed. Reg*. 63583.

to cut and withdraw the mesh (Tracking number 30005250).[459] Another device was provided and cystoscopy equipment was replaced. Repeat cystoscopy showed no mesh in the bladder. Patient was discharged and returned with complaints of dark urine postoperatively and serosanquineous leakage with foley catheter in place. A second surgery was performed the day after the initial procedure and the bladder showed two perforations from the surgery the prior day and a "button hole" in the vagina, with mesh buried underneath the mucosa. The button hole was repaired during the second procedure. The complaint report states that "[i]t does not appear that the device malfunctioned. The bladder perforation and the vaginal 'button hole' would not be due to the direct fault of the device rather it would be due to surgical technique." This conclusion was affirmed by the Medical Director, Dr. C. Owens. Rationale for not reporting this event included "that the reported injury is readily apparent to the clinician, at which point the clinician may either continue with this device, with another device or treatment modality, or completely abort the procedure." Notably, each of these proposed options as to how the clinician could have addressed this event presented potential additional risk to the patient, e.g., impact on safety and effectiveness, extended duration of surgery and thus anesthesia, or re-operation.

As discussed previously, the regulation does not exempt events caused by user error from reporting requirements if an event meets the criteria for MDR reporting. The patient was exposed to extended surgical time and additional risk as a result of removal of the initially-placed implant and placement of a second device. It is notable that the complaint record states that based on "information from the Medical Director the MDR will be reset to reflect that no medical/surgical intervention was needed or performed for the bladder perforation." To the contrary, the "patient was taken to the OR" due to the postoperative complaints and, while the two holes in the bladder were identified and the injury was expected to heal on its own, the "button holed" area of the vagina was repaired. It is important to recall that the TVT system includes not only the polypropylene tape with polyethylene sheath, both of which are attached to two stainless steel needles, but also a stainless steel introducer and rigid catheter guide. As Dr. Axel Arnaud confirmed, "the TVT is essentially a surgical procedure rather than a product," stating that "[m]ost of it is in the surgical approach."[460] Accordingly, user error in the surgical technique is not a basis for determining an event is not MDR-reportable. User error may be the sole cause or only contribute to an MDR-reportable event. MDR reports of adverse events that result from user error are important, because they can serve to alert FDA that improved labeling and/or training may be needed to prevent future injuries. Device injuries resulting from user error may show that the device is misbranded in that it does not have adequate directions for use or adequate warnings.[461]

2. Malfunctions Ethicon Determined Were Not MDR-Reportable

Medical Device Reporting requires that a manufacturer report a malfunction to FDA if the device or a similar device it markets would be likely to cause or contribute to a death or serious injury if the

[459] ETH.MESH.02627532-536: Issue Report (Tracking Number: 30005250).
[460] Dr. Axel Arnaud deposition, July 19, 2013, 138:12-16.
[461] Medical Device Reporting for Manufacturers, Department of Health and Human Services, Public Health Service, Food and Drug Administration, March 1997.

malfunction were to recur.[462] The regulation assumes that a malfunction will recur.[463] FDA has determined that a malfunction is reportable if it meets any one of several criteria, the following of which are applicable to the TVT:

- it causes the device to fail to perform its essential function and compromises the device's therapeutic effectiveness which could cause or contribute to a death or serious injury;[464,465]
- the device involves a long-term implant[466] or involves an implant malfunction that would be likely to cause or contribute to death or serious injury.[467]

"Malfunctions of long-term implants are not routinely or 'automatically' reportable unless the malfunction is likely to cause or contribute to a death or serious injury if it recurs."[468]

Exhibit 4 provides examples of malfunctions that were MDR-reportable in my professional opinion but for which Ethicon did not submit MDR reports to FDA. Specifically, Exhibit 4 provides descriptions of 10 such reports, including the following:

- Eight (8) reports of the mesh fraying or unraveling and/or fragments falling off or the tape becoming particles;[469,470,471,472,473,474,475,476]
- One report of "[a]bout 2mm foreign matter like stone [that] was found at vaginal mucous membrane," suspected by surgeon to be portion of the product that frayed, moved into the vaginal cavity, "became nucleus of the foreign matter and formed a foreign matter like a stone";[477]
- One (1) report of a problem that occurred in three patients, notably, that "the overlap on the sheath came apart exposing the tape and therefore making it difficult to place the tape in the correct position without causing any further trauma to the patient" and in one case having to hold the sheath together, causing concern of possible damage to the tape

[462] 21 CFR § 803.50(a).
[463] Medical Device Reporting: An Overview, April 1996, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA.
[464] Medical Device Reporting: An Overview, April 1996, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA.
[465] Medical Device Reporting for Manufacturers, Department of Health and Human Services, Public Health Service, Food and Drug Administration, March 1997.
[466] Medical Device Reporting: An Overview, April 1996, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA.
[467] Medical Device Reporting for Manufacturers, Department of Health and Human Services, Public Health Service, Food and Drug Administration, March 1997.
[468] FDA Compliance Program Guidance Manual 7382.845, Attachment C.
[469] ETH.MESH.02627350-354: Issue Report (Tracking Number: 30005087).
[470] ETH.MESH.02627669-673: Issue Report (Tracking Number: 30005383).
[471] ETH.MESH.02627517-521: Issue Report (Tracking Number: 30005210).
[472] ETH.MESH.02627780-784: Issue Report (Tracking Number: 30005522).
[473] ETH.MESH.02627494-498: Issue Report (Tracking Number: 30005193).
[474] ETH.MESH.02628220-225: Issue Report (Tracking Number: 10100026906).
[475] ETH.MESH.02628155-160: Issue Report (Tracking Number: 10100023117).
[476] ETH.MESH.02630272-277: Issue Report (Tracking Number: 10100114785).
[477] ETH.MESH.02630120-126: Issue Report (Tracking Number: 10100108279).

(noted in complaint that TVT devices used had "sheath shortened from the 5cm overlap to the 2cm overlap" and that surgery was extended 15 minutes).[478]

In one report of small fragments of Prolene falling off when the mesh was lightly touched, cut, or stretched, it was noted that the surgery was extended 10 minutes. Moreover, this customer was concerned that the mesh fragments would "reject in the body and/or create infections and erosions" and also "about fragments traveling in the body."[479] Thus, it is noteworthy that the "foreign matter like stone" complaint described above was believed by the surgeon to have resulted from a mesh fragment having eroded into the vaginal cavity. This "foreign matter like stone" was observed seven to eight years after TVT implantation.[480] In another report of "tape becoming particles," it was stated that the surgeon notified the patient that "intensive postoperative surveillance" was needed; customer also stated "[t]here is a high probability that this device will not act as intended for the treatment of stress urinary incontinence due to its lake [sic] of mechanical strength. It's the first use of the Blue TVT."[481]

Ethicon's rationale for not reporting these malfunctions as MDRs typically included one or both of the following reasons:

- "Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure."
- "There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure."

In one case, the given rationale included that the event was not reportable because it "*occurred post-procedure* and no actual device malfuntion [sic] is cited,"[482] yet the tape unraveled and became particles; after implantation, the staff remarked there were remaining particles in the box.[483] [Emphasis added.] For another complaint, the rationale for not reporting the event as an MDR included that it "does not indicate that a serious injury occurred, or that medical intervention was required to prevent a serious injury."[484] In the latter case, the "tape frayed from [the] edges," had "less memory and [stayed] stretched during tensioning. Additionally, it was noted that "[b]its of frayed ends may have lodged inside the patient."[485] As discussed previously in this Report, concerning a complaint about "uneven/inconsistent tape width as well as fraying edges," Medical Director Dr. Martin Weisberg stated, "…I don't think we have any idea whether the tape inconsistencies are clinically significant or not…"[486] Thus, it could not be ruled out that this malfunction might compromise the therapeutic effectiveness of the TVT and cause or contribute to a serious injury and, therefore, was MDR-reportable.

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[478] ETH.MESH.02627775-779: Issue Report (Tracking Number: 30005511).
[479] ETH.MESH.02627350-354: Issue Report (Tracking Number: 30005087).
[480] ETH.MESH.02630120-126: Issue Report (Tracking Number: 10100108279).
[481] ETH.MESH.02627517-521: Issue Report (Tracking Number: 30005210).
[482] ETH.MESH.02627669-673: Issue Report (Tracking Number: 30005383).
[483] *Id.*
[484] ETH.MESH.02628220-225: Issue Report (Tracking Number: 10100026906).
[485] *Id.*
[486] ETH.MESH.03905472 at 473-474: Email series April 23-June 6, 2001, initiated by Richard Hu, Johnson & Johnson Medical Taiwan, Re: TVT recommendation from Dr. Alex Wang.

The stated rationales for not reporting the events in Exhibit 4 as MDRs are inconsistent with the FDA-established criteria for MDR reporting of malfunctions described above. Specifically, TVT product labeling (i.e., the IFU) does not caution the TVT user that the mesh may fray and become particles. Further, there is no mention in the product description or instructions for use that mesh fraying or particle loss is normal. Although it was sometimes noted in the event description that there was no adverse patient outcome, these events were product malfunctions and can reasonably be considered to compromise the device's therapeutic effectiveness, which has the potential to necessitate re-operation to remove the device and treat recurrent SUI. One surgeon pointed out (noted above) that "[t]here is a high probability that this device will not act as intended for the treatment of stress urinary incontinence…"[487] Also, it cannot be ruled out that the mesh fragments may cause or contribute to a serious injury longer-term. For these reasons, Ethicon had an obligation to report these malfunctions to FDA in my professional opinion.

A reasonably prudent medical device manufacturer also would have performed due diligence to follow up these events to determine if there were any longer-term sequelae. I found no evidence that Ethicon performed any such actions, and all complaints were closed within less than one month to less than four months, unless reopened due to receipt of complaint sample (one case).[488] Notably, in disregard of the response to a complaint provided by an Ethicon "rep," specifically, that "[u]ntil patient is followed up in a few months time, we won't know if there are any adverse effects ie. Failed procedure at 3 month follow up," the complaint was closed in less than two months from the alert date.[489] FDA requires a manufacturer to make a good faith effort to obtain information about a complaint; the focus of follow-up investigations should be on obtaining information, not on the number of attempts.[490] By its failure to perform meaningful due diligence in following up these complaints to obtain supplemental information on their longer-term outcome, Ethicon violated the standard of care required of a medical device manufacturer.

As regards the complaint of the sheath coming apart and exposing mesh (described above), in which multiple concerns were noted, i.e., about difficulty in placing the tape correctly, further trauma to the patient, and damage to the tape, it is notable that the IFU specifically advises that "[p]remature removal of the sheath may make subsequent adjustments difficult."[491] This complaint represented a product malfunction and reasonably could be considered to compromise the device's therapeutic effectiveness, with the potential to necessitate subsequent medical or surgical intervention.

In summary, Ethicon's determination that the malfunctions included in Exhibit 4 and discussed above were not MDR-reportable was faulty. There was no basis on which Ethicon could reasonably conclude that recurrence of these problems would not be likely to result in serious injury or that the malfunctions did not cause the device to fail to perform its essential function and compromise its therapeutic effectiveness, which could cause or contribute to a serious injury. Based on my synthesis and analysis of the information discussed above and my knowledge, training, and

[487] ETH.MESH.02627517-521: Issue Report (Tracking Number: 30005210).
[488] ETH.MESH.02627669 at 670: Issue Report (Tracking Number: 30005383).
[489] ETH.MESH.02630272: Issue Report (Tracking Number: 10100114785).
[490] Medical Device Reporting for Manufacturers, CDRH, FDA, March 1997.
[491] ETH.MESH.02340471 at 484: Gynecare TVT™ IFU, 10/04.

experience in medical product development and adverse event reporting, a reasonably prudent medical device manufacturer would have reported these events as MDRs and proactively followed up longer-term to assess whether there were any sequelae potentially associated with the discussed TVT malfunctions.

E. FDA Inspection 08/29/2005 – 09/08/2005: Form FDA 483 and Establishment Inspection Report (EIR)

FDA conducted an inspection of Ethicon during August to September 2005 "to follow up on multiple Medical Device Reports (MDRs) involving death and serious injury events."[492] "On 9/8/05, a FDA-483 (Inspectional Observations) was issued to and discussed with Ms. Catherine V. Beath, Worldwide Vice President Quality and Compliance." Significantly, "[t]he inspection revealed an objectionable condition concerning that investigation of MDR reportable complaints did not include a determination of whether the device failed to meet specifications. Investigations conducted for multiple MDR events related to the firm's TVT (Tension Free Vaginal Tape) Device, TVT Obturator, and Thermachoice II Balloon Catheter did not show a determination of whether the device failed to meet specifications. In addition, the records of complaint investigations do not include the determination of the need for corrective and preventive actions."[493]

OPINION #4: TVT System Misbranded Due to Failure to Meet the Postmarket Vigilance Standard of Care and Manage Risk

MDR reporting helps to ascertain the safety profile of the device postmarketing in order to ensure it is safe and effective for its intended use or to initiate timely corrective action if safety or effectiveness concerns arise. Accordingly, as advised in the GHTF guidance titled, "Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative," "[a]s a general principle, there should be a pre-disposition to report rather than not to report in case of doubt on the reportability of an event."[494]

Objective due diligence must be applied to the evaluation of complaint reports in order to manage potentially evolving risks. I reviewed a number of medical reviews of TVT complaints that demonstrated an apparent lack of knowledge and/or understanding of MDR reporting requirements in my professional opinion. To that point, Medical Director Dr. Martin Weisberg testified as follows in response to questions regarding the criteria that qualify an event as reportable to FDA: "That would have to come from our quality department. I don't know what the FDA's rules are."[495] That is an extraordinary admission from a Medical Director who has the responsibility for reviewing events and making determinations that result in MDR-reporting decisions. The contribution of the TVT System as a potential factor in a number of complaints was minimized or negated; for example, events were assessed as technique- or user-related, as due to other

[492] ETH.MESH 07281435 at 437: Ethicon, Inc., Establishment Inspection Report, 08/29/2005 – 09/08/2005.
[493] ETH.MESH 07281435 at 437: Ethicon, Inc., Establishment Inspection Report, 08/29/2005 – 09/08/2005.
[494] GHTF FINAL DOCUMENT: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative, June 29, 1999.
[495] Dr. Martin Weisberg deposition, August 9, 2013, 954:5-955:21.

speculative causes (e.g., erosion due to vaginal atrophy, corticosteroids, etc.), and decision was made there was no device malfunction or injury to the patient in such case as vaginal extrusion of the mesh that bothered the patient and required trimming. Ethicon failed to implement consistently effective and objective due diligence. As a result, MDR reports for MDR-reportable events were not submitted to FDA as required by 21 CFR Part 803, Subpart E.

Most of the MDR reports reviewed were initial reports, with approximately 15% comprising follow-up reports. Ethicon had the responsibility to follow up reported events until resolution or no further information was available as determined through good faith due diligence. In my professional opinion, Ethicon deviated from the standard of care required of a medical device manufacturer by its failures to follow up reports of unresolved adverse events.

By its failure to report MDR-reportable events to FDA, such as those that have been discussed above, Ethicon denied FDA of the knowledge of these events and also physician users and patients of this clinically important information, which has import for product decisions and patient management. FDA depends on the compliance of the manufacturer with MDR reporting requirements for the Agency to be able to perform its role in postmarket surveillance and identifying any potential safety signal(s) that may require corrective action.

As pointed out by then CDRH Director, Office of Compliance, Timothy Ulatowski, MDR reports and complaints are among the principal methods used to assimilate product information and take action as needed.[496] In my professional opinion, Ethicon deviated from the standard of care by its failure to report to FDA a number of adverse events and malfunctions that met the criteria for Medical Device Reporting, rendering the TVT devices misbranded as a result of failure to furnish information requested under Section 519 of the FDCA.[497] The FDA depends on the manufacturer's cooperation and compliance with the Medical Device Reporting regulations to protect the public health.

XI. SUMMATION OF OPINIONS: STANDARD OF CARE AND DEVIATIONS

The FDCA prohibits the introduction into interstate commerce of misbranded devices [FDCA § 301 (a)] and sets forth the circumstances in which a device would be misbranded (FDCA § 502). Ethicon deviated from the required standard of care by misbranding the TVT devices in multiple ways and otherwise violated the standard of care expected of a reasonably prudent medical device manufacturer as specified in my professional opinions below, each of which has been discussed previously in this Report but is summarized here for ease of reference.

OPINION #1: Failure to Conduct Appropriate Testing

The information discussed in this Report concerning the potential for persistent foreign body reaction and chronic inflammation, mesh degradation, cytotoxicity, chronic infection leading to chronic inflammation, and the potential for carcinogenicity highlight numerous potential concerns of TVT mesh implantation about which Ethicon not only failed to warn healthcare practitioners and

[496] Ulatowski TA. Risk Management: A Regulatory Perspective, Presentation, Beijing, October 2008.
[497] FDCA § 502(t).

patients but also failed to investigate through appropriate testing. Summarily, Ethicon failed to perform testing that was critical to learning the long-term safety of the TVT permanent implant and thus fell below the standard of care required of a reasonably prudent medical device manufacturer. Moreover, Ethicon failed to comply with its own credo, specifically, that the company's first responsibility is to the doctors and patients who use Ethicon's products."[498]

OPINION #2: TVT System Misbranded Due to Failure to Warn

Product labeling is a cornerstone of risk management. Its purpose is to provide the user with the information necessary to use the product safely and effectively. Required use information includes indications, effects, routes, methods, and any relevant hazards, contraindications, side effects, and precautions under which the device can be used safely.[499] Labeling that fails to reveal material facts and consequences that may result from product use is considered misleading. Thus, product labeling that fails to include risk information, warnings, and directions important to safe use is considered false and misleading.

TVT devices were misbranded as a result of Ethicon's failure to warn both healthcare providers/physicians and also patients about multiple potential risks known or knowable to Ethicon from the time of product launch. The company knew or should have known of multiple risks associated with the TVT System that were not included in the Instructions for Use (IFU) and patient labeling information. Nor did the patient labeling show fair balance of benefit vs. risk information. Labeling that is false or misleading and does not bear adequate directions for use, including adequate warnings, causes a device to be misbranded.[500,501] In my professional opinion, Ethicon deviated from the standard of care required of a medical device manufacturer by marketing a product that was misbranded because of the stated labeling deficiencies. Further, by its failure to take appropriate actions through labeling to manage risk associated with its product, Ethicon fell below the standard of care for a reasonably prudent medical device manufacturer.

OPINION #3: TVT System Misbranded as a Result of False or Misleading Labeling

The definition of "false or misleading" is not confined to meaning untrue, fraudulent, or deceptive. Labeling can be deemed by FDA to be misleading and in violation of FDA requirements if it proves deceptive to the customer by creating or leading to a false impression in the mind of the reader. Failure to inform the consumer of facts relevant to statements actually made may cause a "false impression," such that labeling that remains silent concerning certain consequences may be as deceptive as labeling that contains extravagant claims.[502]

Ethicon utilized promotional labeling that was false and misleading and failed to reveal material facts. This constituted misbranding. The introduction or delivery for introduction into interstate commerce of any device that is misbranded is a violation of Section 301(a) of the FDCA.[503]

[498] Exhibit T-115 (no Bates number): Johnson & Johnson credo.
[499] 21 CFR § 801.109(d).
[500] FDCA § 502(a), 21 U.S.C. § 352(a).
[501] FDCA § 502(f)(2).
[502] Medical Devices: Labeling Requirements – Misbranding (Available at www.fda.gov).
[503] 21 U.S.C. § 331(a).

Thus, Ethicon deviated from the standard of care required of a medical device manufacturer by the multiple ways in which the TVT device was misbranded, including professional and patient labeling and also promotional labeling that was false and misleading in its representations and/or failed to include known or knowable safety information.

OPINION #4: TVT System Misbranded Due to Failure to Meet the Postmarket Vigilance Standard of Care and Manage Risk

Ethicon failed to implement consistently effective and objective due diligence in the evaluation of complaint reports in order to manage potentially evolving risks, minimizing or negating the contribution of the TVT device as a potential factor in a number of adverse event reports. Thus, MDR reports for MDR-reportable events were not submitted to FDA as required by 21 CFR Part 803, Subpart E. Ethicon also failed to follow up to learn the outcome of adverse events unresolved at the time of reporting or at the time determined not to be MDR-reportable. In my professional opinion, Ethicon deviated from the standard of care by its failure to report to FDA a number of adverse events that met the criteria for Medical Device Reporting, rendering the TVT devices misbranded as a result of failure to furnish information requested under Section 519 of the FDCA.[504] The FDA depends on the manufacturer's cooperation and compliance with the Medical Device Reporting regulations to protect the public health.

XII. CONCLUSIONS

Based on my professional experience, knowledge, and training and my review, evaluation, integration, and synthesis of the information identified and discussed in this Report, including the materials and scientific/medical literature specified in Appendices B and C and information presented in Exhibits 1 through 4, it is my professional opinion, to a reasonable degree of scientific and professional probability, that Ethicon violated those duties required of a reasonably prudent medical device manufacturer.

The TVT System devices were misbranded due to multiple labeling issues, including false and misleading information, inadequate directions for use, specifically, inadequate warnings and information about potential risks. The devices were misbranded due to a failure to reveal material facts as to the consequences that might result from the use of the device. Additionally, the TVT devices were misbranded because of Ethicon's failure to submit MDR reports for a number of adverse events that qualified for reporting under Section 519 of the FDCA.

[504] FDCA § 502(t).

As a consequence of these multiple failures, Ethicon marketed a product that violated safety and ethical standards and, notably, the Johnson & Johnson credo, which begins as follows: "We believe our first responsibility is to the doctors, nurses and patients, to mothers and fathers and all others who use our products and services. In meeting their needs everything we do must be of high quality."[1] Both the physicians using the TVT System devices and the patients in whom these devices were used lacked the necessary information to make an informed decision about the risks versus the benefit of using this device instead of an alternative method of treatment. Accordingly, the standard of care for the protection of the rights, safety, and welfare of patients was violated, thus disrupting the regulatory process and the protections that exist specifically to safeguard the public health.

I reserve the right to amend or supplement this Report in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts.

Peggy Pence, PhD, RAC, FRAPS

October 14, 2013

Date

[1] Exhibit T-115 (no Bates number): Johnson & Johnson credo.

Peggy Pence, PhD, RAC, FRAPS
Expert Witness Report
Ethicon, Inc. Pelvic Repair System,
Products Liability Litigation

Exhibit 1: MAUDE Database/MDR Reports: Most Commonly Reported Adverse Events for GYNECARE TVT™

October 14, 2013

Section 1: Methods and Groupings for Ethicon Tension Free Vaginal Tape MDRs

A. Description of Search Methods for MDR Identification

The Manufacturer and User Facility Device Experience (MAUDE) database (DB) was searched for Medical Device Reports (MDRs) for the "Ethicon" tension-free vaginal tape (TVT).

Simple searches of the MAUDE DB for January 1, 1998, through December 31, 2010, were conducted for the following search terms: "vaginal tape," "tape mesh," "tension free," "EWHU" (Ethicon Women's Heath and Urology), "bladder mesh," "vaginal sling," and "bladder tape." Simple searches were also conducted for the terms "unknown mesh product," "unk mesh," "vaginal mesh," and "sling mesh," but because of the large number of reports, advanced searches had to be conducted for some months.

Catalog numbers in the MDRs were used to determine the products to be included. The catalog numbers included are as follows: 810041, 810041A, 810041B, 810041D, 810041BL, 830041, 830041B, 810051, 810061, 510041, 10041, 530041, and 610041. The last four of these were mostly under the manufacturer name "Medscand." MDRs with unknown catalog numbers were also tabulated.

All such MDRs were reviewed and an Excel Workbook was created to record the information provided about the adverse event(s). As per established conventions, 16-digit report numbers (xxxxxxx-year-xxxxx) indicate that the manufacturer or distributor was the source of the report; seven-digit numbers (xxxxxxx) indicate a user facility was the source of the report, and voluntary reports are preceded by MW (MWxxxxxxx). The Workbook includes the event date, event type, patient outcome, report source, type of report (initial or follow-up), date manufacturer received the event report, and date FDA received the report (to calculate the time between the two dates). Reports with neither a manufacturer narrative nor an event description also are included. Reports where the device malfunctioned before being used on the patient are not included.

B. Reported Adverse Events

The most commonly reported adverse events, defined as adverse events reported in 2% or more MDRs, are shown in Table 1. The total number of most commonly reported adverse events and also the percentage of total MDR reports in which such events were reported are shown. Of note, adverse events related to the urinary system are reported collectively as urinary problems in Table 1. The multiple adverse events represented by "urinary problems" are shown in the listing following Table 1 and are tabulated by year of report date in Section 2 of this exhibit. As regards the other most commonly reported events, because different reporting terms were used, terms were combined as shown following Table 1 for the purpose of this analysis and also are tabulated by year of report date in Section 2 of this exhibit.

Table 1. Ethicon Tension Free Vaginal Tape MDRs: Most Commonly Reported Adverse Events (1999-2010)

Event	n (Reports)	% of total MDRs (1,173)
Urinary Problems	405	34.5%
Erosion	377	32.1%
Pain	291	24.8%
Bleeding	151	12.9%
Sexual Dysfunction	117	10.0%
Organ Perforation	103	8.8%
Infection	82	7.0%
Unspecified Illness/Issues/injuries	67	5.7%
Discharge	54	4.6%
Wound Healing Problems	45	3.8%
Neurological Compromise or Damage	35	3.0%
Scarring	34	2.9%

The terms in the above table were only counted once per report. For instance, if a patient experienced both voiding dysfunction and incontinence, it was counted as one "Urinary Problem." Below is the breakdown of the exact number of occurrences of each symptom.

- Urinary Problems includes the terms: Voiding Dysfunction (265), Incontinence (91), UTI/Cystitis (54), Dysuria (41), Hematuria (16), Bladder Stones (10), Bladder Spasms (6), Acute Renal Failure (4), Overactive Bladder (4), Bladder Obstruction (3), Bladder Calculi (2), Pyuria (2), Bladder Lesion (1), and Kinked Urethra (1).
- Erosion includes the terms: Unspecified Tissue Erosion (138), Vaginal Erosion (116), Bladder Erosion (48), Urethral Erosion (42), Vaginal Wall Erosion (35), Visible Mesh (7), Pelvic Bone Erosion (1), Rectal Erosion (1), Colon Erosion (1), UV Junction Erosion (1), and Mons Pubis Erosion (1).
- Pain includes the terms: Pain (247), Chronic Pain (49), Tenderness/Soreness (17), Pressure (4), and Pain with Defecation (1).
- Bleeding includes the terms: Bleeding/Hemorrhage (109), Hematoma (47), and Blood Clots (3).
- Sexual Dysfunction includes the terms: Dyspareunia (106), and Impaired Physical Relationship (23).
- Organ Perforation includes the terms: Bladder Perforation (60), Bowel Perforation (24), Colon Perforation (7), Intestine Perforation (6), Cecal Perforation (4), Ureter Perforation (2), and Vaginal Perforation (1).
- Infection includes the terms: Unspecified Infection (58), Sepsis/Toxic Shock (6), Peritonitis (5), Necrotizing Fasciitis (4), Yeast Infection (4), Cellulitis (3), Staph Infection (3), Vaginal Infection (2), and E. coli (1).
- Unspecified Illness/Issues/Injuries (67) includes only those terms.
- Discharge (54) includes only that term.
- Wound Healing Problems includes the terms: Delayed/Impaired Healing (41), and Tissue Separation/Dehiscence/Incision Disrupted (4).

- Neurological Compromise or Damage includes the terms: Neurologic Compromise (26), and Nerve Damage (9).
- Scarring includes the terms: Scar Tissue (31), and Unspecified Scarring (3).

Other adverse events reported include the following: Edema/Swelling (18), Fever (18), Deformed Mesh (17), Difficulty Walking (16), Emotional Problems/Quality of Life (16), Fistula (14), Paresthesia (14), Abscess (11), Fatigue/Weakness/No Energy (10), Irritation/Redness/Rash (Erythema) (10), Nausea/Vomiting/Stomach Problems (9), Inflammation (8), Bowel Obstruction (Ileus) (8), Pulmonary Embolism (7), Granuloma/Granulation Tissue (7), Anemia (6), Distended/Rigid Abdomen (6), Blood Pressure Problems (4), Odor (4), Rectocele (4), Vocational/Financial Hardship (4), Pulling/Poking Sensation (4), Fecal Incontinence (4), Difficulty Sitting (4), Acute Abdomen (3), Difficulty Breathing (3), Enterocele (3), Itching (3), Adhesion (2), Allergic Reaction (2), Collapsed Lung (2), Cystocele (2), Type 2 Diabetes (2), Difficulty Sleeping (2), Fibrosis (2), Friction (2), Hernia (2), Seroma (2), White Blood Count Elevated (2), Necrosis (1), Bruising (1), Constipation (1), Crepitus (1), Distended Bowel (1), Eczema (1), Emphysema (1), Fainting (1), Fasciculation (1), Fibroids (1), Hypotension (1), Inflammatory Bowel Disease (1), Internal Wounds (1), Myocardial Infarction (1), Pneumonia (1), Poking Sensation (1), Respiratory Problems (1), Sinus Tract (1), Skin Discoloration (1), Slurred Speech (1), Spotting (1), Stroke (1), Thrombocytosis (1), Tissue Damage (1), Ulcer (1), Thickened Endometrium (1), Vaginal Dryness (1), Vaginal Stone (1), Vascularization (1), and Welts/Hives (1). In addition, reports that did not specify what injuries, illnesses, or issues the patient experienced were tabulated as "Unspecified Illness/Issues/Injuries."

Patient outcomes reported include the following: Not Specified (1,018), Hospitalization (96), Disability (39), Other (39), Life-Threatening (23), and Death (15). Multiple selections were possible, and some reports do not state a patient outcome.

C. Methodology Used for Tabulating Treatments Noted in MDR Reports

For this analysis, a distinction was made between "trimming," which involves cutting of the mesh, usually conducted in a physician's office, and "surgery," which includes a more extensive procedure that was usually conducted in an operating room, may have included mesh modification, and may have been conducted to treat complication(s) from the implant surgery. "Surgery" also includes both partial and complete mesh removal and "excision" of mesh, as well as surgery without any further explanation and the mention of "surgery and revisionary procedures." This analysis distinguishes between "surgery" (one or more surgeries that have already taken place) and "follow up surgery planned" (for reports where it is stated that surgery is planned). For those reports related to surgery complications (see below), "surgery" as a treatment option is only marked if the complication was treated in a subsequent surgery, not if it was addressed during the primary surgery, unless the complication was more severe and another specialist was called in to treat the complication, or the surgery was changed from a vaginal procedure to an open abdominal surgery.

If a report stated the reason for surgery, that information was captured in the DB. If a report mentioned complications occurring during surgery (e.g., organ perforation) or a symptom occurring after surgery (e.g., erosion) that was possibly caused by the mesh not being implanted

properly (e.g., surgeon thinks he tightened mesh too much), it is marked in the DB as an "unspecified" surgical complication, i.e., meaning that the reason for the complication was speculative only.

In addition to the surgical and "trimming" treatment options discussed above, other treatments were captured. The number of patients who received each treatment type was totaled.

D. Reported Treatments

As regards follow-up surgery, 348 (30.0%) of the MDRs reported that the patient had undergone one follow-up surgery, 177 (15.1%) reported that the patient had undergone two or more follow-up surgeries, and 94 (8.0%) reported that the patient would undergo surgery as a result of the reported adverse events for a total of 619 (52.8%) patients who required surgery or for whom surgery was planned.

Treatments other than surgery and planned surgery included the following: Catheter (119), Antibiotics (107), Cystoscopy (94), Other Prescription Drugs (86), Blood Transfusion (27), Pain Medication (23), Hormone Therapy (20), Hematoma Drained (17), Physical Therapy (13), Trimming (13), Suturing (9), Urethral Dilation (8), Injections (7), Interstim (neuromodulation therapy) (7), Cream (7), Drains/Irrigation (6), Mobilization of Urethra (6), Urethroscopy (6), Vaginal Tamponade (6), Vaginal Packing (5), Compression (4), Embolization (4), Pulled Down Tape (4), Steroids (4), Nerve Block (3), Cystourethroscopy (2), Bed Rest (1), Cauterization (1), Intubation (1), Medical Wick (1), and Wound Vacuum (1). Treatments categorized under "Unspecified" treatments in this report are those that did not include any further information in the MDRs. Also, throughout this analysis, not every single treatment was counted; instead, classes of treatments were counted. For example, any number of antibiotics described for a particular report was counted only once.

E. Initial Reports and Follow-up Reports

The majority of reports located by the MAUDE DB search were labeled "Initial." While the FDA received most initial reports within 30 days of manufacturer receipt of the report, there were 87 reports with a somewhat longer reporting interval. Sixty-seven (67) reports were reported within 31 to 44 days, six (6) were reported within 45 to 60 days, eight (8) were reported within 61 to 90 days, and seven (7) reports were reported between 91 to 212 days. A total of 101 reports did not have an entry for "date manufacturer received."

F. Other Information Captured

If there was another surgical procedure performed at the time of implantation of the mesh, this was tabulated and the procedure was noted as a "possible complicating procedure." If any symptom(s) persisted at the time the report was submitted, this was noted as "problem persists." In addition, if a follow-up surgery was planned at the time the report was submitted, it was also tabulated as "problem persists."

For Voluntary reports that could be matched to a Manufacturer report, only the Manufacturer report was entered. All Manufacturer reports were entered, even if two or more reports used identical language and had identical information, suggesting that they were duplicate reports. The occurrence of such reports, however, was infrequent. Also, reports with information collected from literature were all included, even if they used the same wording, because these articles represented multiple patients. The potentially duplicate reports were noted as such.

Attempts were made to distinguish between surgical complications that were either "device-related," "technique-related," or both. Where a distinction could not be made, the complication was tabulated as an "unspecified" surgical complication.

If a surgical complication extended the duration of the initial surgery, it was noted. If the vaginal tape broke or malfunctioned during surgery and an additional device was used—either in addition to the tape or instead of it—it was noted and also tabulated as "extended duration of surgery."

When there was a period of over one year between implantation and the emergence of symptom(s), it was tabulated.

Several of the earlier reports mentioned a "tunica vaginalis testis" procedure and/or tape, which would suggest a male patient. This is likely an error in the interpretation of the abbreviation "TVT," so these reports were still included.

G. Limitations of Search Methods

It is possible that additional adverse events were missed during this search, due, primarily, to the variable and unknown manner in which any manufacturer might code or report a specific event and the potential differing product representations under which a device may be entered into the MAUDE DB. However, previous experience has proven the same search methods to be effective in capturing almost all of the relevant MDRs.

Exhibit 1 - Section 2
Tabulations by Year of Report Date

Urinary Problems Details																
Year	n (Reports)	Voiding Dysfunction	Incontinence	UTI Cystitis	Dysuria (painful urination)	Hematuria (blood in urine)	Bladder Stones	Bladder Spasms	Overactive Bladder	Acute Renal Failure	Bladder Obstruction	Bladder Calculi	Pyuria (pus in urine)	Bladder Lesion	Kinked Urethra	Total Events by Year
2010	45	28	17	11	1	3	2	1	0	0	0	0	0	0	0	63
2009	41	22	13	16	0	0	0	0	0	0	0	0	0	0	0	51
2008	39	27	10	4	1	2	0	0	1	0	3	0	0	0	0	48
2007	11	6	3	0	0	2	0	0	0	0	0	2	0	1	0	14
2006	6	1	4	0	0	0	1	0	0	0	0	0	0	0	0	6
2005	21	14	8	3	0	2	0	0	0	1	0	0	0	0	0	28
2004	35	23	7	6	6	1	0	1	0	2	0	0	1	0	0	47
2003	44	31	11	5	5	3	3	1	0	0	0	0	0	0	0	59
2002	110	74	4	3	27	2	3	1	3	0	0	0	1	0	1	119
2001	28	21	7	4	0	1	0	2	0	0	0	0	0	0	0	35
2000	14	9	5	2	0	0	1	0	0	1	0	0	0	0	0	18
1999	11	9	2	0	1	0	0	0	0	0	0	0	0	0	0	12
Totals	405	265	91	54	41	16	10	6	4	4	3	2	2	1	1	500
% Total Reports (1173)	34.5%	22.6%	7.8%	4.6%	3.5%	1.4%	0.9%	0.5%	0.3%	0.3%	0.3%	0.2%	0.2%	0.1%	0.1%	42.6%

Erosion Details												
Year	n (Reports)	Vaginal Erosion	Unspecified Tissue Erosion	Bladder Erosion	Urethral Erosion	Pelvic Bone Erosion	Rectal Erosion	Colon Erosion	UV Junction Erosion	Mons Pubis Erosion	Mesh Visible	Total Events by Year
2010	102	12	80	5	5	1	0	1	0	0	0	104
2009	58	21	27	10	1	0	1	0	0	1	0	61
2008	35	17	11	2	4	0	0	0	0	0	1	35
2007	10	5	2	4	1	0	0	0	0	0	1	13
2006	13	6	4	2	1	0	0	0	0	0	0	13
2005	18	8	3	3	5	0	0	0	0	0	0	19
2004	32	14	4	6	8	0	0	0	0	0	0	32
2003	40	24	4	8	3	0	0	0	0	0	1	40
2002	46	34	0	6	7	0	0	0	0	0	2	49
2001	9	5	1	0	2	0	0	0	1	0	1	10
2000	11	5	2	1	3	0	0	0	0	0	1	12
1999	3	0	0	1	2	0	0	0	0	0	0	3
Totals	377	151	138	48	42	1	1	1	1	1	7	391
% Total Reports (1173)	32.1%	12.9%	11.8%	4.1%	3.6%	0.1%	0.1%	0.1%	0.1%	0.1%	0.6%	33.3%

Pain Details							
Year	n (Reports)	Pain	Chronic Pain	Tenderness/ Soreness	Pressure	Pain with Defecation	Total Events by Year
2010	83	82	11	0	1	0	94
2009	46	35	15	0	0	0	50
2008	29	17	11	2	0	0	30
2007	9	7	1	1	0	0	9
2006	6	5	0	1	0	0	6
2005	10	8	1	1	0	0	10
2004	15	11	1	2	2	1	17
2003	25	20	5	1	0	0	26
2002	43	39	3	4	0	0	46
2001	11	11	0	2	0	0	13
2000	11	9	1	3	1	0	14
1999	3	3	0	0	0	0	3
Totals	291	247	49	17	4	1	318
% Total Reports (1173)	24.8%	21.1%	4.2%	1.4%	0.3%	0.1%	27.1%

Bleeding Details					
Year	n (Reports)	Bleeding/ Hemorrhage	Hematoma	Blood Clots	Total Events by Year
2010	12	10	1	0	11
2009	13	12	1	0	13
2008	12	11	4	0	15
2007	5	3	2	0	5
2006	2	2	0	0	2
2005	6	5	2	0	7
2004	12	7	4	1	12
2003	8	6	3	0	9
2002	53	38	15	0	53
2001	7	4	4	0	8
2000	5	3	2	1	6
1999	16	8	9	1	18
Totals	151	109	47	3	159
% Total Reports (1173)	12.9%	9.3%	4.0%	0.3%	13.6%

Sexual Dysfunction Details				
Year	n (Reports)	Dyspareunia	Impaired Physical Relationship	Total Events by Year
2010	27	27	2	29
2009	28	26	8	34
2008	12	7	6	13
2007	2	2	1	3
2006	1	1	0	1
2005	3	3	1	4
2004	8	8	1	9
2003	2	2	0	2
2002	25	25	0	25
2001	5	2	3	5
2000	4	3	1	4
1999	0	0	0	0
Totals	117	106	23	129
% Total Reports (1173)	10.0%	9.0%	2.0%	11.0%

Organ Perforation Details									
Year	n (Reports)	Bladder Perforation	Bowel Perforation	Colon Perforation	Intestinal Perforation	Cecal Perforation	Ureter Perforation	Vaginal Perforation	Total Events by Year
2010	8	4	0	4	0	0	0	0	8
2009	2	2	0	0	0	0	0	0	2
2008	1	1	0	0	0	0	0	0	1
2007	2	1	1	0	0	0	0	0	2
2006	2	1	0	1	0	0	0	0	2
2005	7	1	2	0	3	1	0	0	7
2004	22	15	4	0	1	0	2	0	22
2003	17	5	8	0	2	2	0	0	17
2002	24	18	4	1	0	1	0	1	25
2001	5	3	2	0	0	0	0	0	5
2000	6	3	2	1	0	0	0	0	6
1999	7	6	1	0	0	0	0	0	7
Totals	103	60	24	7	6	4	2	1	104
% Total Reports (1173)	8.8%	5.1%	2.0%	0.6%	0.5%	0.3%	0.2%	0.1%	8.9%

Infection Details											
Year	n (Reports)	Unspecified Infection	Sepsis/ Septic Shock	Peritonitis	Necrotizing Fascitiis	Yeast Infection	Cellulitis	Staph Infection	Vaginal Infection	E. coli	Total Events by Year
2010	14	11	1	0	0	2	0	0	1	0	15
2009	12	12	0	0	0	0	0	0	0	0	12
2008	17	12	0	0	0	1	0	3	1	0	17
2007	3	2	0	0	1	0	0	0	0	0	3
2006	2	1	0	0	1	0	0	0	0	0	2
2005	7	0	1	3	0	1	1	0	0	0	6
2004	5	5	0	0	0	0	0	0	0	0	5
2003	5	3	1	1	1	0	0	0	0	0	6
2002	10	8	1	0	0	0	1	0	0	0	10
2001	0	0	0	0	0	0	0	0	0	0	0
2000	4	2	1	0	1	0	1	0	0	1	6
1999	3	2	1	1	0	0	0	0	0	0	4
Totals	82	58	6	5	4	4	3	3	2	1	86
% Total Reports (1173)	7.0%	4.9%	0.5%	0.4%	0.3%	0.3%	0.3%	0.3%	0.2%	0.1%	7.3%

Wound Healing Problems Details				
Year	n (Reports)	Delayed or Impaired Healing	Tissue Separation, Dehiscence, Disrupted Incision	Total Events by Year
2010	1	1	0	1
2009	1	1	0	1
2008	0	0	0	0
2007	3	1	2	3
2006	0	0	0	0
2005	0	0	0	0
2004	4	3	1	4
2003	0	0	0	0
2002	31	31	0	31
2001	0	0	0	0
2000	5	4	1	5
1999	0	0	0	0
Totals	45	41	4	45
% Total Reports (1173)	3.8%	3.5%	0.3%	3.8%

Neurologic Compromise or Damage Details				
Year	n (Reports)	Neurologic Compromise	Nerve Damage	Totals by Year
2010	16	16	0	16
2009	13	10	3	13
2008	3	0	3	3
2007	2	0	2	2
2006	0	0	0	0
2005	0	0	0	0
2004	0	0	0	0
2003	0	0	0	0
2002	0	0	0	0
2001	0	0	0	0
2000	1	0	1	1
1999	0	0	0	0
Totals	35	26	9	35
% Total Reports (1173)	3.0%	2.2%	0.8%	3.0%

Scarring Details				
Year	n (Reports)	Scarring (unspecified)	Scar Tissue	Total Events by Year
2010	17	0	17	17
2009	13	1	12	13
2008	1	1	0	1
2007	0	0	0	0
2006	1	1	0	1
2005	0	0	0	0
2004	0	0	0	0
2003	2	0	2	2
2002	0	0	0	0
2001	0	0	0	0
2000	0	0	0	0
1999	0	0	0	0
Totals	34	3	31	34
% Total Reports (1173)	2.9%	0.3%	2.6%	2.9%

Patient Outcome Details							
Year	Not Specified	Hospitalization	Disability	Other	Life-Threatening	Death	Total Events by Year
2010	68	5	7	5	2	1	88
2009	62	17	15	17	3	1	115
2008	84	18	7	6	2	0	117
2007	27	4	5	3	1	0	40
2006	31	3	1	1	0	1	37
2005	54	6	1	1	8	2	72
2004	86	3	1	0	1	1	92
2003	96	6	2	2	3	2	111
2002	219	2	0	2	1	2	226
2001	107	3	0	0	0	1	111
2000	145	5	0	1	2	2	155
1999	39	7	0	1	0	2	49
Totals	1018	79	39	39	23	15	1213
% Total Reports (1173)	86.8%	6.7%	3.3%	3.3%	2.0%	1.3%	103.4%

Peggy Pence, PhD, RAC, FRAPS
Expert Witness Report
Ethicon, Inc. Pelvic Repair System,
Products Liability Litigation

Exhibit 2: TVT™ Patient Brochures – Risk Information Provided

October 14, 2013

EXHIBIT 2: TVT™ Patient Brochures – Risk Information Provided

highlighted areas indicate that a change in wording was made from the previous version

Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
Freedom From Stress Urinary Incontinence – It's within your control. ETH.MESH.08003173-174, 179-180	2001	Q: What are the risks associated with GYNECARE TVT tension-free support? A. All surgical procedures present risks. Although rare, complications associated with the treatment include injury to blood vessels of the pelvic sidewall and abdominal wall, difficulty urinating, and bladder and bowel injury. For a complete description of risks, see the adverse events section of the attached product information. **CONTRAINDICATIONS** As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the PROLENE polypropylene mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy. **WARNINGS AND PRECAUTIONS** **Do not use GYNECARE TVT device for patients who are on anticoagulation therapy.** **Do not use GYNECARE TVT device for patients who have a urinary tract infection**. Users should be familiar with surgical technique for bladder neck suspensions before employing the GYNECARE TVT device. It is however important to recognize that GYNECARE TVT is different from a traditional sling procedure in that the tape should be located without tension under mid-urethra. Acceptable surgical practice should be followed for the GYNECARE TVT device as well as for the management of contaminated or infected wounds. Incontinence repair using the GYNECARE TVT device should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and proper passage of needles will minimize risks. Retropubic bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from hospital. Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should be gently pushed

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		into the Foley catheter so that the catheter guide does not extend into the holes of the Foley Catheter. When removing the rigid catheter guide, open the handle completely so that the catheter remains properly in place. Do not remove the plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with minimal tension under mid-urethra. PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material. The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Post-operatively the patient is recommended to refrain from heavy lifting and/or exercise (i.e. cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria, bleeding or other problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded. Do not contact the PROLENE mesh with any staples, clips or clamps as mechanical damage to the mesh may occur. Do not resterilize GYNECARE TVT device. Discard opened, unused devices. ADVERSE REACTIONS Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair. Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination. Over correction, i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.
Stress Urinary Incontinence in Women – What YOU can do about it ETH.MESH.08003181 at 194-196	2004	What are the risks? All medical procedures present risks. Although rare, complications include difficulty urinating, injury to blood vessels of the pelvic sidewall and abdominal wall, and bladder and bowel injury. For a complete description of risks, see the adverse events section of the attached product information. CONTRAINDICATIONS (Same as Previous) WARNINGS AND PRECAUTIONS Do not use these devices for patients who are on anticoagulation therapy. Do not use these devices for patients who have a urinary tract infection. Users should be familiar with surgical technique for urethral suspensions and should be adequately trained in these procedures before employing these devices. Acceptable surgical practice should be followed for these procedures as well as for the management of contaminated or infected wounds. These procedures should be performed with care to avoid large vessels, nerves bladder and bowel. Attention to patient anatomy and correct passage of the device will minimize risks. Bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from hospital. Do not remove the plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with no tension under the mid-urethra. PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material.

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		Do not perform these procedures if you think the surgical site may be infected or contaminated. Since no clinical information is available about pregnancy following a suburethral sling procedure with these devices, the patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical information is available about vaginal delivery following these procedures, in case of pregnancy cesarean section should be considered. Postoperatively, the patient should be advised to refrain from heavy lifting and/or exercise (e.g., cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria, bleeding or other problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded. As with other incontinence procedures, de novo detrusor instability may occur following these procedures. To minimize this risk, make sure to place the tape tension-free in the mid-urethral position. Do not contact the PROLENE mesh with any staples, clips or clamps as mechanical damage to the mesh may occur. Do not resterilize any single-use devices or components. Discard opened, unused devices. Prophylactic antibiotics can be administered according to the surgeon's usual practice. WARNINGS & PRECAUTIONS – additional for GYNECARE TVT/GYNECARE TVT with abdominal guides The abdominal guide should not be used to pull the interlocked system upward toward the abdomen. Ensure there is a snug connection between the guide

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		and coupler and the coupler and TVT needle. Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should then be gently pushed into the Foley catheter so that the catheter guide does not does not extend into the holes of the Foley catheter. When removing the rigid catheter guide, open the handle completely so that the catheter retains properly in place. WARNINGS & PRECAUTIONS – additional for GYNECARE TVT Obturator System Although bladder injury is unlikely to occur with this technique, cystoscopy should be performed at the discretion of the surgeon. Transient leg pain lasting 24-48 hours may occur and can usually be managed with mild analgesics. ADVERSE REACTIONS (Same as Previous)
Stress Urinary Incontinence in Women – What YOU can do about it ETH.MESH.08003197, 210-212	2005	What are the risks? (Same as Previous) CONTRAINDICATIONS (Same as Previous) WARNINGS AND PRECAUTIONS Do not use these devices for patients who are on anti-coagulation therapy. Do not use these devices for patients who have a urinary tract infection. Users should be familiar with surgical technique for urethral suspensions and should be adequately trained in these procedures before employing these devices. Acceptable surgical practice should be followed for these procedures as well as for the management of contaminated or infected wounds. These procedures should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to patient anatomy and correct passage of the device will minimize risks. Bleeding may occur postoperatively. Observe for

EXHIBIT 2: TVT™ Patient Brochures – Risk Information Provided

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		any symptoms or signs before releasing the patient from hospital. Do not remove the plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with no tension under mid-urethra. PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material. Do not perform these procedures if you think the surgical site may be infected or contaminated. Since no clinical information is available about pregnancy following a sub-urethral sling procedure with these devices, the patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical information is available about vaginal delivery following these procedures, in case of pregnancy delivery via cesarean section should be considered. Postoperatively, the patient should be advised to refrain from heavy lifting and/or exercise (e.g., cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can usually return to other normal activity after one or two weeks. Should dysuria, bleeding or other problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded. As with other incontinence procedures, de novo detrusor instability may occur following these procedures. To minimize the risk, make sure to place the tape tension-free in the midurethral position. Do not contact the PROLENE mesh with any staples, clips or clamps as mechanical damage to the mesh may occur.

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		Do not resterilize any single-use devices or components. Discard opened, unused devices. Prophylactic antibiotics can be administered according to the surgeon's usual practice. WARNINGS & PRECAUTIONS – additional for GYNECARE TVT/GYNECARE TVT with abdominal guides (Same as Previous) WARNINGS & PRECAUTIONS – additional for GYNECARE TVT Obturator System (Same as Previous) ADVERSE REACTIONS (Same as Previous)
The Choice to end Stress Urinary Incontinence – Find out how to stop urine leakage like Bonnie did ETH.MESH.08003215, 228-230	2006	What are the risks? (Same as Previous) CONTRAINDICATIONS (Same as Previous) WARNINGS & PRECAUTIONS (Omitted) ADVERSE REACTIONS (Omitted)
The Choice to end Stress Urinary Incontinence – Find out how to stop urine leakage like Bonnie did ETH.MESH.08003231, 244-245	2006	What are the risks? All medical procedures present risks. As with all procedures of its type, there's a risk of injury to the bladder and surrounding organs. For a complete description of risks, see the attached product information. CONTRAINDICATIONS (Same as Previous) WARNINGS & PRECAUTIONS Do not use the GYNECARE TVT Family of Products for patients who are on anti-coagulation therapy. Do not use the GYNECARE TVT Family of Products for patients who have a urinary tract infection.

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		Bleeding or infection may occur post-operatively. Transient leg pain lasting 24-48 hours may occur and can usually be managed with mild analgesics after a GYNECARE TVT Obturator system. Since no clinical information is available about pregnancy following sub-urethral sling procedure with the GYNECARE TVT Family of Products, the patient should be counseled that future pregnancy may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical information is available about vaginal delivery following sub-urethral sling procedure with the GYNECARE TVT Family of Products, in case of pregnancy, delivery via cesarean section should be considered. Post-operatively, refrain from heavy lifting and/or exercise (e.g. cycling, jogging) for at least three to four weeks and to refrain from intercourse for at least one month. The patients can usually return to other normal activity after one or two weeks. Contact your surgeon immediately if there is burning sensation during urination, unusual bleeding, problems voiding or other problems. ADVERSE REACTIONS Punctures or lacerations or injury to vessels, nerves, bladder, urethra, or bowel may occur during instrument passage and may require surgical repair. Improper placement of the TVT device may result in incomplete or no relief from urinary incontinence or may cause urinary tract obstruction.
The Choice to end Stress Urinary Incontinence – Find out how to stop urine leakage like Bonnie did ETH.MESH.08003247 at 260-262	2007	Same as Previous
The Choice to End Stress Urinary Incontinence – One day you have urine leakage. The next day you don't. End of Story.	2007	Same as Previous

EXHIBIT 2: TVT™ Patient Brochures – Risk Information Provided

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Title of Brochure & Bates #	**Date**	**Risks (wording from each brochure included below)**
ETH.MESH08003263, 276-278		
The Choice to End Stress Urinary Incontinence- Find out how to stop urine leakage like Bonnie did ETH.MESH.03458123 at 136-137	March 26, 2008 (Approval Date)	Same as Previous
Treatment Options for Stress Urinary Incontinence- Stop coping. Start living. ETH.MESH.08003279, 292-294	2008	What are the risks? All surgical procedures present some risks. Complications associated with the procedure include injury to blood vessels of the pelvis, difficulty urinating, pain, scarring, pain with intercourse, bladder and bowel injury. There is also a risk of the mesh material becoming exposed. Exposure may require treatment. For a complete description of risks, see the attached product information. Synthetic mesh is a permanent medical device implant. Therefore, you should carefully discuss the decision to have surgery with your doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat your condition. CONTRAINDICATIONS (Same as Previous) WARNINGS & PRECAUTIONS (Same as Previous) ADVERSE REACTIONS Punctures or lacerations or injury to vessels, nerves, bladder, urethra, or bowel may occur during instrument passage and may require surgical repair. Transitory local irritation at the wound site and a transitory foreign body response may occur. This could result is extrusion, erosion, fistula formation or inflammation. Improper placement of the TVT device may result in incomplete or no relief from urinary incontinence or may cause urinary tract obstruction.
Treatment Options for Stress Urinary Incontinence Stop coping.	2009	Same as Previous

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
Start living. ETH.MESH.08003303, 316-318		
Stress Urinary Incontinence- Stop coping. Start living. ETH.MESH.06087471-472	2010	What are the Risks? (Omitted) CONTRAINDICATIONS (Same as Previous) WARNINGS & PRECAUTIONS Do not use GYNECARE TVT Family of Products for patients who are on anti-coagulation therapy. Do not use GYNECARE TVT Family of Products for patients who have urinary tract infection. Bleeding or infection may occur post-operatively. Transient leg pain lasting 24-48 hours may occur and can usually be managed with mild analgesics after GYNECARE TVT Obturator or GYNECARE TVT ABBREVO procedure. Since no clinical information is available about pregnancy following sub-urethral sling procedure with the GYNECARE TVT Family of Products, the patient should be counseled that future pregnancy may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical information is available about vaginal delivery following sub-urethral sling procedure with GYNECARE TVT Family of Products, in case of pregnancy, delivery via cesarean section should be considered. Post-operatively, refrain from heavy lifting and/or exercise (e.g. cycling, jogging) for at least three to four weeks and refrain from intercourse for one month, The patient can usually return to other normal activity after one or two weeks. Contact your surgeon immediately if there is burning sensation during urination, unusual bleeding, problems voiding or other problems. ADVERSE REACTIONS Punctures or lacerations or injuries to vessels, nerves, bladder, urethra, or bowel may occur during instrument passage and may require surgical repair.

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		Improper placement of the TVT device may result in incomplete or no relief from urinary incontinence or may cause urinary tract obstruction. Transitory local irritation at the wound site and a transitory foreign body response may occur. This could result in extrusion, erosion, fistula formation or inflammation.
Gynecare TVT Tension-free Support for Incontinence ETH.MESH.06087513-514	2010	Same as Previous
Treatment Options for Stress Urinary Incontinence-Stop coping. Start living. ETH.MESH.08003295, 301-302	2011	What are the risks? All surgical procedures present some risks. Complications associated with sling procedures with synthetic mesh include injury to blood vessels of the pelvis, nerve damage, difficulty urinating, pain with intercourse and bladder or bowel injury. There is also a risk of the mesh material becoming exposed into the vaginal canal. Mesh exposure can be associated with pain during intercourse for the patient and her partner. Exposure may require treatment such as vaginal medication or removal of the exposed mesh, which may be performed in the office or operating room. Synthetic mesh is a permanent medical device implant. Therefore, you should carefully discuss the decision to have surgery with your doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat your condition. CONTRAINDICATIONS (Same as Previous) WARNINGS & PRECAUTIONS (Same as Previous) ADVERSE REACTIONS (Same as Previous)
Stop Coping. Start Living. What You Should Know About Stress Urinary Incontinence ETH.MESH.09744858-863	2012	WHAT ARE THE RISKS? **Risks Common to All Pelvic Surgeries:** Risks for all pelvic surgeries include pain with intercourse, pelvic pain, development of urinary incontinence or voiding difficulties, hemorrhage (bleeding) or hematoma (collections of blood in the pelvis), injury

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Title of Brochure & Bates #	Date	Risks (wording from each brochure included below)
		to abdominal organs including bowel, urinary tract infection, bladder injury, wound healing problems, fistula (holes between bladder or bowel and the vagina), injury to ureters (tubes bringing urine from kidneys to bladder), pelvic abscess formation and nerve damage. **Complications Associated with Synthetic Mesh:** There is a risk of the mesh material becoming exposed into the vagina. Mesh exposure can be associated with pain during intercourse for you and your partner. Exposure may require treatment, such as vaginal medication or removal of the exposed mesh, which may be performed in the office or operating room. There is a risk of infection, inflammation, vaginal scarring and mesh contracture (mesh shortening due to scar tissue). Pelvic pain, or pain with intercourse, may occur and may resolve with time. There is a risk of developing urinary incontinence or difficulty urinating. Synthetic mesh is a permanent medical device implant. Therefore, you should carefully discuss the decision to have surgery with your surgeon and understand the benefits and risks of mesh implant surgery before deciding how to treat your condition. CONTRAINDICATIONS (Same as Previous) WARNINGS & PRECAUTIONS (Same as Previous) ADVERSE REACTIONS (Same as Previous)

Peggy Pence, PhD, RAC, FRAPS
Expert Witness Report
Ethicon, Inc. Pelvic Repair System,
Products Liability Litigation

Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

October 14, 2013

Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
Erosions/Extrusions				
30001906 ETH.MESH. 02622556-560	January 30, 2002	April 4, 2002	Complaint: 6 months after surgery with TVT the patient noted a 2.5x2.5mm vaginal mesh extrusion on the left lateral side. The patient has no pain and remains continent and pleased with the procedure. She is 64 and is not on hormone replacement therapy. She had a previous hysterectomy and no other significant medical history. No concomitant procedures were performed. One pass was made with each needle. There were no bladder perforations. The physician will leave the mesh as is unless the patient becomes symptomatic. At that point he may use topical estrogen or trim or excise the mesh.	Not reportable – provide rationale for not reporting: Not reportable in that, as per the medical review, this is a case of minimal, asymptomatic vaginal extrusion. Therefore, the patient will not require any medical or surgical intervention to correct the extrusion or to otherwise preclude serious injury or permanent damage with regards to the structure or function of the vaginal area. The event is not indicative of any product malfunction.
30002788 ETHMESH. 02623207-210	August 21, 2002	November 19, 2002	At the request of field rep Rob Wagner the medical director spoke with [REDACTED] on 8/21/2002 [REDACTED] has placed 6 TVT?s [sic] since completing training. He performed a procedure on a patient approximately 6 weeks ago. The tape was placed via the vaginal route. At this time the vagina appears to be healed but a loop of tape approximately 3 cm is noted in the vagina. [REDACTED] will trim the tape. He will contact me if this is not successful or if the patient?s [sic] incontinence returns. He noted that the patient had an episode of coughing during her immediate post-op period. He attributes the tape extrusion to the coughing. I agree.	Report to FDA is not required: Physician attributes the tape extrusion to an episode of coughing that the patient experienced following the procedure.
30003086 ETH.MESH. 02623595-599	October 10, 2002	January 17, 2003	It was reported via the medical director that at the request of field representative Michelle Pulver I spoke to [REDACTED] saw a patient who had a sling procedure with TVT inserted	Report to FDA is not required: Not reportable in that there was no device malfunction. The patient was treated by

§ Includes de novo, new, recurrent, worsening, return of, ongoing; urgency, urgency leak, urge frequency, frequency, urge incontinence, stress incontinence, stress urinary incontinence, urinary incontinence, urge incontinence, incontinence

Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			approximately 4/5/2000. The patient had a vagina extrusion, which was treated by trimming the visible tape. She still "feels the tape and it bothers her." [REDACTED] will inject the site with local anesthesia and, based on the response, may resect one arm of the tape.	trimming the tape which is not considered an additional invasive procedure. There was no injury to the patient.
30003576 ETH.MESH. 02625497-501	April 24, 2003	June 9, 2003	Received message from sales rep via 800 line regarding TVT device. Physician identified a vaginal mesh extrusion, possibly due to vaginal incision that was closed ineffectively.	Report to FDA is not required: Not reportable. Vaginal extrusion of mesh following a sling procedure with TVT can be the result of inadequate closure of the vaginal mucosa, vaginal wall trauma during the healing process (e.g., resumption of intercourse prior to healing), estrogen deficient mucosa, among other reasons. It is not the result of the device itself.
30005489 ETH.MESH. 02627743-747	June 20, 2005	July 26, 2005	Originated from PC# 30005429. Customer does not like color change. Affiliate advised received letter from gynaecologist at hospital stating "The general principle is that if the TVT procedure is perfomed [sic] in conjunction with other procedures e.g. anterior or posterior repair or even vaginal hysterectomy the general consensus is to insert the tape first but to leave loose and tighten it only when the repairs have been performed. This means that the tape and sheath are dangling in the operative field for quite a while and I have noticed that the plastic sheath frequently frays under these circumstances." "I remain concerned about tape erosions since you chose to dye the tape. I was performing a TVT for 18 months with the undyed tape with no erosions. I have had 4 or 5 since you have changed the tape to blue. I have now changed the	Not Reportable - Document rationale why not to report: Not reportable in that neither serious nor device malfunction which could lead to a serious injury have occurred. Event reported is a customer preference issue. It does not affect the efficacy of the product or present a risk for serious injury to the patient.

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Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			way I suture the midline vaginal incision using one vicryl continuous reverse locking sutures rather then [sic] previous vicryl rapid as the suture material stays longer in the vagina. Even so some tape erosions are occurring lateral to the midline. I am sure the dying procedure is changing the property of the tape. It is less soft, pliable and flexible."	
30005305 ETH.MESH. 02627592-597	April 6, 2005	July 20, 2005	Received a Synergy form from an Affiliate with a TVT complaint: "Description: Extrusion of the device Treatment of stress urinary incontinence with associated pelvic floor repair + Hysterectomy + posterior perinea repair. Use of the associated 'GYNEMESH PS' device Ref GPSL lot TKB065 (refer to complaint # 5882) Event Description box of the AFSSAPS form filled by the customer to CA (AFSSAPS): Date JAN xx? 2005 - extrusion of a piece of tape 'GYNEMESH SOFT' trough the vaginal cul-de-sac (end/bottom) scare in a the pelvic floor repair Consequences: NEW SURGERY Consequences box of the AFSSAPS form filled by the customer to CA (AFSSAPS): The patient point out pains to the surgeon several months after the procedure. Visits need to follow-up and perform treatment. Phone conversation with the surgeon: Patient 50 years old approx. 90 kg approx. a full 1 square centimeter appears through the hysteroscopy scare in the vaginal cul-de -sac (end/bottom). During a visit, the surgeon attempted to withdraw of a small piece of the mesh and to trim the edges of the wound, unfortunately this was too painful. A re-operation performed 3-4 weeks ago with general anesthesia to trim the edges	Not Reportable - Document rationale why not to report: Not a reportable event in that event occurred post-procedure and no actual device malfunction is cited or indicated. There is no evidence to suggest that the device itself caused any impairment or damage to body function or body structure.

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Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			of the wound. Follow up visit planned at the end of this month." [represented exactly as entered in Issue Report]	
Erosion/Extrusion & Incontinence [§]				
30003463 ETH.MESH. 02625397-403	March 19, 2003	May 7, 2003	Received product complaint checklist via e-mail from affiliate regarding TVT. Surgeon reported that during a re-operation due to return of incontinence two years post original TVT procedure, he identified that TVT tape from prior surgery had eroded into vagina. Surgeon removed this tape.	Report to FDA is not required: Not a reportable event in that no serious injury occurred. Extrusion of TVT tape may be the result of many factors including an inadequately estrogenized vaginal mucosa, trauma, improper closure and other things but not the direct fault of the device. Appropriate management is the removal of the exposed portion. The patient had the same clinical presentation as before the procedure, and this condition is not considered life threatening or serious to the patient.
30005380 ETH.MESH. 02627651-655	May 18, 2005	June 23, 2005	From file #30005338. Received a call on the 800 line from a sales rep with a customer complaint regarding a TVT Device. It was reported that the patient had a vaginal hysterectomy and sling procedure done on 05/19/2004. Since that time the patient has had a series of ongoing post operative problems. Within the first two weeks of post op, the patient developed De novo Urge Incontinence. The patient was started on Detrol medication. She has had multiple bladder infections within the past year with no previous history of bladder infections prior to the procedure. She also developed two vaginal tape erosions. The right vaginal side was noticed in the office in 12/2004. The Doctor tried to	Not Reportable - Document rationale why not to report: Not a reportable event in that there was no device malfunction or serious injury occurred. Persistent urinary stress incontinence following a sling procedure with TVT is likely the result of sub optimal placement of the device and is not likely due to the failure of the device itself. The patient would have the same clinical presentation as before the procedure and this condition is not considered life threatening or serious to the patient.

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Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			medically manage her and then the Doctor did an inoffice [sic] procedure on 02/2005 and cut out approximately 1 cm of the TVT tape. During a visit on 04/2005 it was then noticed that the left lateral vaginal wall also had the tape coming through. The Doctor cut out a piece from the left side of the tape and resewed the vaginal mucous on top. The patient continues to complaint [sic] of urge incontinence and also of stress urinary incontinence. Urodynamcs [sic] test was done in the office and the test did not show stress urinary incontinence. The physician has referred the patient to a Urologist on 05/09/2005. Received Medical Review from Dr. Owens: Urge incontinence is sometimes unmasked or a transient known occurrence after TVT placement. When it is transient it is usually self limiting. This is not unique to the TVT device as any sling procedure can have this occur after. Mesh exposure is influenced by many factors including an inadequately estrogenized vaginal mucosa, trauma, improper closure and other things, but not the direct fault of the mesh as this can occur with any permanent implant. It is not clear if this patient has urodynamic stress incontinence prior to surgery. If she did it is known that TVT is not 100% effective. If she did not this could contribute to her ongoing incontinence which is not SUI according to the urodynamics noted in the complaint.	
Erosion/Extrusion & Dyspareunia or Partner Pain During Intercourse				
30002949 ETH.MESH.	September 20, 2002	December 23, 2002	The medical director was contacted by [REDACTED] a urologist who told me about an 51 year old woman who had mesh extrusion into	Report to FDA is not required: Physician theorized that corticosteroids may

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Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
02623462-465			the vagina causing dyspareunia 2 months after having a sling procedure utilizing TVT. The exposed portion of the tape was cut vaginally and the patient's symptoms resolved. [REDACTED] noted that there was no extrusion at the time of postoperative examination and theorized that corticosteroids may have been responsible for thinning of the vaginal wall and the tape extrusion.	have been responsible for thinning of the vaginal wall and the tape extrusion. No device malfunction was reported.
30003353 ETH.MESH. 02625246-49	February 13, 2003	April 21, 2003	At the request a [sic] field representative Scott Jones I spoke to [REDACTED] on February 14, 2003. [REDACTED] performed a sling procedure with TVT in early January, 2003. At the time of the post operative visit, [REDACTED] noticed that in the right fornix of the vagina some fibers from edge of the TVT tape could be seen extruded [sic] through the vaginal mucosa. The patient was having no symptoms. [REDACTED] plans to trim the exposed mesh without making any incisions and treating the patient with estrogen cream. This appears to be extrusion of the fringed edge of them [sic] mesh through the vaginal mucosa. This may have resulted from surgical technique, but the contribution of the device itself cannot be ruled out. I spoke to [REDACTED] on 4/17/2003. She told me that the patient continues to have exposed tape in the vaginal fornix and that it is causing pain to her husband when they have intercourse. She plans to excise the tape in the surgical center.	Report to FDA is not required: Not a reportable event in that there was no device malfunction. The patient was treated by trimming the tape which is not considered an additional invasive procedure. There was no injury to the patient.
30003425	March 5, 2003	June 17, 2003	Received faxed complaint from affiliate with report from physician describing erosion of TVT	Report to FDA is not required:

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Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
ETH.MESH. 02625316-320			tape into the vagina. Tape was originally inserted on 12/16/2003. Patient and partner were aware of something jagged in vagina over the weekend of 2/23/2003-2/24/2003 and saw the physician on 2/28/2003. The physician examined the patient, found TVT tape protruding into the vagina. The physician excised the protruding tape and returned it for evaluation.	Not reportable in that there was no device malfunction. The patient was treated by trimming the tape which is not considered an additional invasive procedure. There was no injury to the patient.
30003797 ETH.MESH. 02625722-725	July 11, 2003	September 9, 2003	At the request of field representative Dana Harris, I spoke to [REDACTED] on 7/15/2003. [REDACTED] performed a TVT on a 37-year-old patient approximately 3 months prior to our conversation. The patient's husband now complains of pain during intercourse. [REDACTED] found a few prongs of mesh protruding through the vaginal mucosa. He plans to excise them in the office. This is a case of vaginal extrusion of TVT mesh. In a patient this age, this can be a result of trauma from early return to intercourse or other vagina trauma. It can also occur if the mesh was not positioned flatly beneath the mucosa, which could be the result of surgical technique. [REDACTED] will notify me if trimming the mesh is not successful.	Report to FDA is not required: Not a reportable event in that no device malfunction occurred. In the case where a surgeon trims the visible tape, this would not be considered an invasive procedure and does not pose as an injury or risk to the patient. This would not be considered an injury with the treatment rendered.
30005209 ETH.MESH. 02627513-516	March 1, 2005	March 17, 2005	Received an e-mailed report from Medical Affairs with a physician complaint regarding TVT: "I received a call from [REDACTED] has a 40 something year old patient who 2.5 months ago had a cystocele repair, rectal sphincter repair and TVT placed vaginally. [REDACTED] states that he made the vaginal incision and then used the trocar as he normally does. What was different in this case is the tape was not place [sic] into the incision it actually was placed	Not Reportable - Document rationale why not to report: Not a reportable event in that event occurred post-procedure and no actual device malfunction is cited. There is no evidence to suggest that the device itself caused any impairment or damage to body function or body structure. Post-operative mesh exposure can occur as a result of multiple

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			lateral to the incision on top of the mucosa. At this point he incised the area around the tape and tried to bury the tape as best as he could. At one week follow up the incision was fine. At 6 weeks later during intercourse the husband felt and got scratched by the TVT. The patient then was able to feel the tape when she palpated it. [REDACTED] has the patient on Prmarin [sic] and antibiotic ointment. In discussing the case with [REDACTED] the reason for the mesh exposure is most likely due to surgical technique related to inadequate closure and depth of mesh placement. [REDACTED] agreed. [REDACTED] will consult with a local physician in town for management consultation or referral as this is his first complication. [REDACTED] stated that thought TVT's mesh was absorbable and would have disappeared by now."	factors. The event did not occur in the EU and does not indicate a problem with any similar CE marked device.
Erosion/Extrusion & Incontinence[§] & Dyspareunia or Partner Pain During Intercourse				
30001311 ETH.MESH. 02621834-839	April 13, 2001	October 10, 2001	The procedure was uneventful and not unusual. The patient was continent and pleased with the procedure until approximately 2.5 weeks after surgery at which time she developed pelvic pain and recurrent SUI. The patient had been compliant with the doctor's recommendations regarding resumption of activities. Upon examination, [REDACTED] found a small edge of mesh protruding through the vaginal mucosa about 1.5cm left lateral to the vaginal incision. 2-3mm of uneven mesh edge was visible. Lateral to this, the doctor could palpate mesh going up into the retropubic space in the usual fashion. On the right, the mucosa was intact, but while the mesh could be palpated going up into	Not reportable – provide rationale for not reporting: Not reportable in that the mesh breakage did not cause or contribute to a serious injury or death.

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			the retropubic space laterally, no mesh could be palpated in the midline. The urethra appears hypermobile. The doctor's conclusion was that the mesh broke in the midline, accounting for the palpated findings and the recurrent SUI. [REDACTED] recalls no visible defect in the mesh and no mishandling of the mesh. She places a rubber shod clamp (one click) on the mesh/sheath during placement and adjustment, but doubts that this would have compromised the mesh. She did deliberately place the mesh "a little loose" in order not to obstruct the elderly woman's urethra. [REDACTED] thinks it is possible but unlikely that SUI is solely from excessive looseness of the mesh. At this point the patient desires no further treatment. She will be followed expectantly. If the mucosa does not cover the exposed mesh, [REDACTED] will excise the exposed portion.	
Erosion/Extrusion & Incontinence[§] & Perforation/Puncture				
30004870 ETH.MESH. 02627146-150	September 24, 2004	October 12, 2004	Received a call on the 800 line from a sales rep with a physician complaint regarding TVT. He reported that the doctor left him a voicemail stating she would like to report a TVT complication. The TVT was placed in August 2004. No other event details known at this time. Received a call from [REDACTED] via the 800 line with additional information. The original procedure was performed on 08/10/2004. [REDACTED] inadvertently punctured the bladder during the procedure. She removed the device and placed a second one. The patient complained of urinary retention on 08/12/2004.	Not reportable – Document rationale why not to report: Not a reportable event in that no serious injury or device malfunctioned [sic] occurred in this event. No medical intervention was provided for the bladder perforation and per the Medical Director the etiology of the bladder entry was technique related and also related to the fact that the patient had a history of previous surgery that may also have contributed.

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			Post-void residuals were followed, UTI was ruled out, and the patient was managed with Ditropan. A cystoscope performed yesterday revealed that there was a vaginal erosion of tape and "something pressing on the bladder," which is causing frequency and incontinence. [REDACTED] did not know what was pressing on the bladder. The current plan is for the sling to be removed on 10/16/2004... Dr. Neto also reported that the cystoscope also identified that there were fragments of mesh in the bladder from the original inadvertent bladder perforation... Received an email message (attached to file) from Dr. Owens with notice of the complaint and medical review: "Spoke to [REDACTED] at [REDACTED] performed a TVT on a patient with initials [REDACTED] on August 10, 2004. During the procedure the bladder was entered on the left side. The sling was then placed on the right side without difficulties, however, during cystoscopy she noted the entry of the TVT into the bladder on the left side. It was removed and then replaced without difficulties. The right side was without problems. The patient was then sent home with a foley and asked to return the next day for foley removal and to check post void residuals. The patient had retention at that time and therefore the foley was replaced and the patient sent home over the weekend with the foley in place. The patient then returned two days later on Monday and the foley was	

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			removed. She had some retention that required her to move her body in certain positions in order to void. A couple of days later she developed urge and infrequency. A urinary tract infection was ruled out. The patient then had a cystoscopy performed by a urologist and he saw pieces of the TVT in the bladder and a suburethral erosion in the vaginal mucosa with a finger like "something", maybe a hematoma, compressing down on the left side of the bladder. The urologist plans to remove the TVT in about a week. The patient now has urgency and incontinence. [REDACTED] feels like the pieces in the bladder are not erosions rather pieces that were left behind when she removed it when it entered the bladder. [REDACTED] will keep me posted on future developments... "The etiology of the bladder entry was technique related and also related to the fact that the patient had a history of previous surgery which may have also contributed. The vaginal erosion of TVT tape may be the result of many factors including an inadequately estrogenized vaninal [sic] mucosa, trauma, improper closure and other things, but not the direct fault of the device as this can occur with any permanent implant.	
Incontinence[§]				
30005291 ETH.MESH. 02627572-576	April 20, 2005	June 7, 2005	From file #30005290. Received email from an affiliate with a customer complaint regarding a TVT Device. "It was reported that the surgeon felt the bleeding is more than usual and it stopped after stitching up a vaginal incision. Therefore the surgeon closed the operation. It was found the	Not Reportable - Document rationale why not to report: Not a reportable event in that there was no device malfunction or serious injury occurred. Persistent urinary stress

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			blood pressure was decreased and she had vomited at this night. As the CT scan found a hematoma at the retroperitoneum of the patient, the surgeon decided to open and clear off the hematoma. The patient transfused because the bleeding was 200 cc or more. The patient was discharged from hospital, but she is still suffering from incontinence." ...It is known that although TVT is highly effective it is not 100% effective. This is not a complication of surgery rather a known possibility after surgery since the cure rate is not 100%.	incontinence following a sling procedure with TVT is likely the result of sub optimal placement of the device and is not likely due to the failure of the device itself. The patient would have the same clinical presentation as before the procedure and this condition is not considered life threatening or serious to the patient.
10100080174 ETH.MESH. 02629301-306	September 25, 2008	December 9, 2008	Complaint received via email from the TVT World Registry with notification of an adverse event. The patient has a underwent [sic] a sling procedure in which TVT was used. Postoperatively on 07/01/2008 it was noted that the patient is experiencing urge incontinence. This event is ongoing at this time. As a result, the patient is being treated medically. The surgeon has indicated that this event is not product related but is possibly procedure related. (TVT World Wide Observational Registry for Long Term Data: Protocol # 300-06-006, Patient ID #025-013-[REDACTED]).	Not Reportable - Document rationale why not to report: Post-operative urge incontinence without urodynamic/cystometric abnormality may only be considered temporary functional disturbance, rather than permanent impairment of a body structure or function. Any 'medical intervention' for the reported 'urge incontinence' therefore may not be considered to preclude a serious patient injury.
10100084516 ETH.MESH. 02629444-450	December 18, 2008	January 30, 2009	Complaint received via email from the TVT World Registry with notification of an adverse event. The patient underwent a sling procedure in which TVT was inserted on 03/18/2008. On 09/16/2008 the patient developed urgency and urgency leak just before 3 month follow up interventiioon [sic]. The patient was started on	Not Reportable - Document rationale why not to report: The current information in the file does not indicate any permanent impairment of a body function or structure underlying the reported urgency/urge incontinence (onset

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Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			solifenacin at the 6 month visit. This has resolved the symptoms completely. The patient remains on solifenancin [sic]. The event is listed as resolved on 12/18/2008. No product is available to be returned for evaluation. The surgeon has indicated that this event was possibly related to the product and possibly related to the procedure. (TVT World Wide Observational Registry for Long Term Data: Protocol #300-06-006, Patient ID 058-045-[REDACTED]).	three months post sling procedure). The use of a muscarinic antagonist (Solifenacin) is mostly for managing the symptoms rather than to preclude any serious injury to the patient. The urinary symptoms have since resolved. There is no clinical evidence to show any relationship among the urinary symptoms, the TVT sling and its placement procedure in the current file.
10100087185 ETH.MESH. 02629507-512	January 29, 2009	February 12, 2009	WCQ received email from TVT World Registry with notification of adverse event for patient # 058-037[REDACTED] enrolled in study protocol 300-06-006 (TVT-World Wide Observational Registry for Long-Term Data) regarding a TVT. The patient underwent a TVT procedure under general Anaesthesia on January 15, 2008. On July 31, 2008, the patient presented with recurrent stress incontinence. The patient reported persistent leakage at six month visit. At the 12 month visit requested repeat surgery. The re-operation is booked for February 3, 2009. Medical Intervention was taken. At this time, the event is still ongoing. The doctor has stated that there were no intra-operative complications. The surgeon states that this is possibly product related and procedure related. He also states that the device did not malfunction. There was no concomitant surgery during the procedure.	Not Reportable - Document rationale why not to report: Not a reportable event. The current information indicated stress urinary incontinence recurrence after a suburethral sling procedure. Another incontinence surgery has apparently been completed. A recurring pre-existing condition may not be considered a permanent impairment of a body structure/function related to a device/device placement procedure. The additional incontinence surgery therefore should not be considered to preclude a serious injury. The re-operation is to address a condition existed before the initial surgery.
10100091213 ETH.MESH. 02629641-646	March 19, 2009	July 9, 2009	The complaint received via email from the TVT World Registry with notification of an adverse event. The patient underwent a Sling Procedure in which TVT was inserted on 11/11/2008. The patient developed recurrent incontinence in	Not Reportable - Document rationale why not to report: Medical/Surgical treatment to remedy SUI recurrence after an initial sling procedure

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			February, 2009. The patient is scheduled for Urodynamics Testing. The date of this testing is unknown at this time. The surgeon has indicated that medical intervention was taken, and that the event is ongoing. The surgeon has not indicated what medical invention was performed. No product is available for evaluation. The surgeon has indicated that this event was possibly related to the product, and possibly related to the procedure. (TVT World Wide Observational Registry for Long Term Data: Protocol # 300-06-006, Pt/ ID# 058-0790[REDACTED])	may not be considered an intervention to preclude any permanent injury. Rather, either approach is to address the pre-existing stress incontinence.
10100095923 ETH.MESH. 02629757-762	June 11, 2009	July 16, 2009	Complaint received via email from the TVT World Registry with notification of an adverse event. The patient underwent a TVT sling procedure on 01/06/2009. Post operatively, the patient presented with urgency and urinary leakage on 03/10/2009. The patient has been placed on oral anticholinergics. The event is listed as ongoing. No product is available to be returned for evaluation. The surgeon indicated that this event was possibly related to the study product, and possibly related to the study procedure. (TVT World Wide Observations Registry for Long Term Data: Protocol 300-06-006. Patient ID# 058-086-[REDACTED]).	Not Reportable - Document rationale why not to report: A suburethral sling neither treats nor causes urinary urgency or urge incontinence. In the absence of any urodynamic and laboratory test results, we are unable to determine the actual cause of the patient's post-operative experience. The current information does not indicate any permanent impairment of a body structure or function occurred, or any intervention to preclude serious injury to the patient has been rendered. The use of anticholinergic may only be considered to manage the symptoms with the current available information. Should additional information indicate otherwise, the medical review will be updated.
10100097363 ETH.MESH. 02629799-805	July 9, 2009	July 28, 2009	Complaint received via email from the TVT World Registry with notification of an adverse event. The patient underwent a TVT sling procedure on 02/10/2009. Post operatively, the	Not Reportable - Document rationale why not to report: The available information in the file seems

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Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			patient presented with worsening of urgency incontinence on 02/24/2009. The patient was known to have detrusor overactivity pre-operatively. She commenced on Solifenacin 5/10 mg on 07/09/2009. The event is listed as ongoing. No product is available to be returned for evaluation. The surgeon indicated that this event was possibly related to the study product, and possibly related to the study procedure. (TVT World Wide Observations Registry for Long Term Data: Protocol 300-06-006. Patient ID 058-091–[REDACTED]).	to imply that the 'urge incontinence' existed before the sling procedure. A suburethral sling procedure neither treats nor causes urge incontinence. Therefore the "worsening urge incontinence" may not be considered permanent impairment of a body structure or function by our product. The use of an anti-cholinergic may not be considered an intervention to preclude serious injury caused by our product.
10100107247 ETH.MESH. 02630091-095	November 26, 2009	December 10, 2009	Complaint received via email from the TVT World Registry with notification of an adverse event. It was reported that patient 058-08[REDACTED] has new urgency. Start date: 08/26/2009. Intervention: Medical. The patient commenced on anticholingergic [sic] medication on 11/26/09. Outcome: Ongoing. Reported to be possibly related to the study product. Reported to not be related to the study procedure. Serious adverse event: Yes, medical intervention to prevent permanent impairment to body structure or body function. [sic] The device did not malfunction.	Not Reportable - Document rationale why not to report: Urgency and frequency are descriptive terms of one's urinary sensations and may or may not be associated with actual urine leakage or involuntary loss. Urge incontinence is a term for sudden urine loss due to experiences of urgency and/or frequency. All three can be common presentations in several conditions such as urinary tract infection, detrusor instability, neurological disturbance, or interstitial cystitis. In the absence of any clinical evidence to suggest the association among urgency/frequency, urge incontinence, and any of the above conditions, it should be considered transient rather than permanent impairment of a body function or structure. In addition, the use of anticholinergics or antimuscarinics without a clear clinical rationale at this stage is considered

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				empirical rather than targeted to preclude permanent injury.
Dyspareunia or Partner Pain During Intercourse				
10100101495 ETH.MESH. 02629940-945	September 11, 2009	September 22, 2009	It was reported by the caller that following the Sling procedure the patient did well following the procedure, but four to five months after the procedure the patient started having pain. The pain was vaginal pain that escalated to pain with intercourse and point tenderness at the bladder neck. This is all the information that is available at this time.	Not Reportable - Document rationale why not to report: Not a reportable event in that event occurred post-procedure and no actual device malfunction is cited or indicated. There is no evidence to suggest that the device itself caused any impairment or damage to body function or body structure. The current information in the file does not indicate that the described patient event was a permanent impairment of a body structure or function. No intervention to preclude any serious injury appears to be rendered.
Perforation/Puncture				
30005250 ETH.MESH. 02627532-536	March 24, 2005	June 7, 2005	Received an email from the Medical Director regarding a TVT complaint. "Received a call from Bart Patterson 800-401-3458. On March 24, 2005 [REDACTED] performed a TVT procedure 3/24/05. After the first needle placement cystoscopy was performed and nothing was seen. When the needle was withdrawn there was a gush of fluid. Cystoscopy was performed and there was mesh in the bladder. At this point decision was made to cut and withdraw the mesh. Another device was provided to the hospital for placement. Before placement of the second device cystoscopy equipment was replaced due to poor lighting and cytoscopy was performed. This revealed no mesh in the bladder. A foley catheter was placed. The patient was discharged and	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported injury is readily apparent to the clinician, at which point the clinician may either continue with this device, with another device or treatment modality, or completely abort the procedure.

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			today returned with complaints of dark urine post operatively and serous sanguineous leakage with the foley in place. [REDACTED] did not know where it was coming from. A urologist was consulted. A second surgery was performed today and the bladder showed 2 perforations from yesterday and there is a 'button hole' in the vagina. The mesh was buried underneath the mucosa. The patient was taken out of the OR with a suprapubic catheter. It does not appear that the device malfunctioned. The bladder perforation and the vaginal 'button hole' would not be due to the direct fault of the device rather it would be due to surgical technique."	
10100010018 ETH.MESH. 02627859-864	September 16, 2005	October 18, 2005	Affiliate advised via Synergy that the "It was reported by the hospital that during a TVT procedure, the surgeon perforated the bladder." "TVT device was removed, and the patient is [sic] will have the procedure done at a later date. Patient is reported to be in good condition and has been discharged from the hospital." Product being returned for evaluation. Bladder perforation is an expected complication in retropubic sling procedures. It was diagnosed and remedied in a timely manner and will not likely result in patient sequellae. There was no device malfunction nor was the design of the device responsible for this incident.	Not Reportable - Document rationale why not to report: In the case of a puncture or stab wound to the bladder, once the sharp is removed from the bladder, the wall will close around the wound sealing it. No medical intervention or repair would be required and bladder function would be preserved. Therefore, this would not normally meet serious injury criteria and not be reportable as an adverse event.
10100057431 ETH.MESH. 02628643-649	September 18, 2007	January 15, 2008	Received email from Medical Affairs with notification of adverse event regarding patient #013-003[REDACTED] enrolled in study protocol 300-06-006 (TVT-World Wide Observational Registry for Long-Term Data). It	Not Reportable - Document rationale why not to report: In the case of a puncture or stab wound to the bladder, once the sharp is removed from

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			was reported that "incidental cystotomy". Action taken: Intervention - Surgical. Outcome is ongoing. Not related to the product. Not related to the procedure. Not a serious adverse event. It is reported that the device did not malfunction. Received email from Doctor with the following information: 1. Hospital that the initial surgery was performed - Inova Fairfax Hospital 2. What was the size and the location of the perforation - the perforation was in the right bladder dome, the diameter of the sling introducer 3. When in the procedure did the perforation occur and what instrument was being used when perforation occurred? The original TVT device was being used. The perforation occurred during sling placement. 4.Please indicate any medical or surgical intervention required to repair the perforation - no intervention required other than overnight catheter drainage 5. Was the repair performed during the initial surgery or was the patient brought back to OR? n/a 6. Was the procedure completed successfully with the same device? Is the device implanted or was it removed? the procedure was completed successfully with the same device 7. What was the product code and lot number of the device implanted? lot #3017819, product 810041 BL 8. If the product was a TVT Secur, what position	the bladder, the wall will close around the wound sealing it. No medical intervention or repair would be required and bladder function would be preserved. Therefore, this would not normally meet serious injury criteria and not be reportable as an adverse event.

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Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			was the device placed (U or hammock position)? na 9. Were there any concomitant procedures being performed? laparoscopic supracervical hysterectomy 10. Was there any extended hospitalization? 2 nights 11.Patient current condition - stable 12. Any future plans for treatment? no 13.Patient demographics (Initials / ID, Age or DOB, weight, Gravidity / Parity) [REDACTED] 165 lbs, g1 p1 14. What was the pre-op diagnosis, if incontinence, what type was it, how long of a history? sui, 4 yrs 15.Any pre- existing medical conditions - GERD, depression 16. Will the device be returned for evaluation? no 17. Was the product reprocessed before use on patient? - only the reusable introducer 18. Any additional information - none	
Other				
30005147 ETH.MESH. 02627410-413	February 11, 2005	April 15, 2005	Received an e-mail message from Medical Affairs with an affiliate's report of a possible TVT allergy. A consultant, [REDACTED] reported that a patient claims to have an ongoing allergic reaction to her TVT tape. The procedure had been done in early September. It is unknown at present whether TVT or TVT-O had been used. The patient complains of tingling sensations in her groin, thighs, and mouth. She has self medicated with Clorphenamine antihistamine and antibiotics, which she reports has helped, but the patient	Not Reportable - Document rationale why not to report: Not a reportable event in that event occurred post-procedure and there is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure. Post-operative tingling sensations can occur as a result of multiple factors. The mesh in TVT is hypoallergenic and there is no evidence that it causes allergies. The patient's symptoms

§ Includes de novo, new, recurrent, worsening, return of, ongoing; urgency, urgency leak, urge frequency, frequency, urge incontinence, stress incontinence, stress urinary incontinence, urinary incontinence, urge incontinence, incontinence

Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			wants the tape removed. Additional information is pending.	are improving with medication.
30005157 ETH.MESH. 02627418-423	February 16, 2005	June 2, 2005	Received email from affiliate with a customer complaint regarding a TVT Device. "A TVT used in patient and patient had hematoma. The doctor had contacted the preceptor, Dr. Kalbfleich regarding this case and the hematoma. This is the only information available at the moment, more details to follow. The product is not being returned for analysis." ...3. How did the bleed occur? Needle hit a vessel 4. What was the source of the bleed? broken blood vessel 5. What was the size of hematoma? 8-10cm 6. Was the hematoma drained or did it resolve on its own? it is being left, monitored to resolve on its own 7. Was a blood transfusion required? not sure 8. What medical or surgical intervention was required? no 9. Did the event extend the patients stay or cause a hospitalization? yes 10. Any additional event details - The incident happened when passing the needle on the left side of the patient and the bladder was perforated on the first passing. The needle was removed and passed again and that is when the vessel was hit. Still has catheter. According to [REDACTED] the patient has other problems that are unresolved including a possible fistula... Although this complaint has been determined not MDR reportable J&J Canada has determined that	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure.

§ Includes de novo, new, recurrent, worsening, return of, ongoing; urgency, urgency leak, urge frequency, frequency, urge incontinence, stress incontinence, stress urinary incontinence, urinary incontinence, urge incontinence, incontinence

Exhibit 3: MDR-Reportable Complaints, Specifically Serious Injury, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description (including pertinent information per Medical Review)	Rationale for Not Reporting
			this complaint is reportable as a Canadian MDR. File updated accordingly.	

[§] Includes de novo, new, recurrent, worsening, return of, ongoing; urgency, urgency leak, urge frequency, frequency, urge incontinence, stress incontinence, stress urinary incontinence, urinary incontinence, urge incontinence, incontinence

Peggy Pence, PhD, RAC, FRAPS
Expert Witness Report
Ethicon, Inc. Pelvic Repair System,
Products Liability Litigation

Exhibit 4: MDR-Reportable Complaints, Specifically Malfunction, Determined by Ethicon to be "Not Reportable"

October 14, 2013

Exhibit 4: MDR-Reportable Complaints, Specifically Malfunction, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description	Rationale
30005087 ETH.MESH. 02627350-354	January 10, 2005	March 10, 2005	Received an e-mailed report from an affiliate with a physician complaint regarding TVT: "Small fragments of white and blue prolene is falling of when light touching, cutting or stretching the mesh. The customer claims that this did not occur when the mesh was white. The customer fair that the fragments will reject in the body and/or create infections and erosions. He also claim the blue fragments can create miss coloring in the skin incision. The customer is also worried about fragments traveling in the body. The customer require answers on all questions before he continue to perform approx 100 TVT's per year." Surgery time was extended 10 minutes with no adverse patient outcome. [represented exactly as entered in Issue Report]	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure.
30005383 ETH.MESH. 02627669-673	May 23, 2005	October 12, 2005	Received email from an affiliate with a customer complaint regarding a TVT Device. "Unraveling and tape became particles. After implantation of the device the staff discovered that there was remaining particles in the box. Device implanted without problems." No consequence. [represented exactly as entered in Issue Report]	Not Reportable - Document rationale why not to report: Not a reportable event in that event occurred post-procedure and no actual device malfuntion [sic] is cited. There is no evidence to suggest that the device itself caused any impairment or damage to body function or body structure.
30005210 ETH.MESH. 02627517-521	March 11, 2005	May 19, 2005	Received an email from an Affiliate with a TVT-B complaint. “This complaint disclosed to AFSSAPS by the customer stated: No stated clinical consequences for the time being. The post-operative complications National survey form (refer to http://agmed.sante.gouv.fr/htm/10/mv/enquete/en	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with this device, with

Exhibit 4: MDR-Reportable Complaints, Specifically Malfunction, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description	Rationale
			quete.htm) to be filled in by the surgeon patient notified by the surgeon [REDACTED]. Patient notified by the surgeon of the need to schedule an intensive postoperative surveillance." Unraveling and tape became particles. This complaint disclosed to AFSSAPS by the customer stated: "The prolene tape became partially unmeshed after the delivery according to the IFU. There is a high probability that this device will not act as intended for the treatment of stress urinary incontinence due to its lake of mechanical strength. It's the first use of the Blue TVT." After questions asked to the survey nurse, it's the "tape becoming particles" phenomenon that occurred at the edge of the tape of the emerging remaining tape further to the unraveling when sheath removal was performed." No adverse patient outcomes. [represented exactly as entered in Issue Report]	another device or treatment modality, or completely abort the procedure.
30005522 ETH.MESH. 02627780-784	August 12, 2005	October 14, 2005	Customer reports that the device had frayed during use. Removed from patient, and replaced with another device used successfully to complete procedure. No adverse patient outcome. Device available for return.	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may continue with this device, another device or treatment modality, or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment, or damage to body function or body structure.
30005511	August 5, 2005	August 19, 2005	Affiliate reports "On three separate occasions on three different patients [REDACTED] was using	Not Reportable - Document rationale why not to report:

Exhibit 4: MDR-Reportable Complaints, Specifically Malfunction, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description	Rationale
ETH.MESH. 02627775-779			the TVT devices that have had the sheath shortened from the 5cm overlap to the 2cm overlap. On each occasion the overlap on the sheath came apart exposing the tape and therefore making it difficult to place the tape in the correct position without causing any further trauma to the patient. On the third occasion [REDACTED]len [sic] had to hold the sheath in place to prevent it from coming apart and she was concerned that by doing so she was possibly damaging the tape [REDACTED] has over 5 years experience in performing TVT procedures and in average performs approx 80 procedures per annum and has not experienced this problem before, therefore we can only presume that the shortening of the sheath is causing the problem" No adverse patient outcome. No product being returned. Surgery extended 15 minutes.	Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may continue with this device, another device or treatment modality, or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment, or damage to body function or body structure.
30005193 ETH.MESH. 02627494-498	February 28, 2005	April 20, 2005	Received email from an affiliate with a customer complaint regarding a TVT Device. "Unraveling and tape became particles. No consequence. The hospital is very upset to see the blue snow in the patient and request a certificate that nothing changes vs. the TVT classic."	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure.
10100026906 ETH.MESH. 02628220-225	May 30, 2006	September 8, 2006	Australia reports via Synergy that the "Surgeon noted bits of tape frayed from edges. Noted tape has less memory and stay stretched during tensioning. Tape remained implanted in patient	Not Reportable - Document rationale why not to report: Not a reportable in that the event does not

Exhibit 4: MDR-Reportable Complaints, Specifically Malfunction, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description	Rationale
			and tape ends returned for product enquiry. Bits of frayed ends may have lodged inside the patient." No adverse outcome.	indicate that a serious injury occurred, or that medical intervention was required to prevent a serious injury. The reported malfunction is readily apparent to the clinician, at which points the clinician may either continue with another device, or treatment modality or completely abort the procedure.
10100023117 ETH.MESH. 02628155-160	April 4, 2006	July 26, 2006	Received email from an affiliate with a customer complaint regarding a TVT Device. "Mesh too soft, frayed more than usual, colour [sic] too dark." Not MDV reportable. No adverse patient outcome.	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure.
10100108279 ETH.MESH. 02630120-126	October 2, 2009	January 21, 2010	An email was received from an affiliate with a customer complaint regarding TVT. It was reported that "About 2mm foreign matter like stone was found at vaginal mucous membrane. The surgeon chipped the foreign matter vaginally from vaginal mucous membrane with a cotton swab. The product was placed near at vaginal mucous membrane as well. The surgeon suspects the portion of the product frayed and it moved into the vaginal cavity then the fibra became nucleus of the foreign matter and formed a foreign matter like a stone. The product was used on the patient around 2001 to 2002, patient is female, 60 years old. We have no patient's	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point, the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure.

Exhibit 4: MDR-Reportable Complaints, Specifically Malfunction, Determined by Ethicon to be "Not Reportable"

Issue Report Tracking # (Bates #s)	Alert Date	Close Date	Event Description	Rationale
			information ID#, initials, weights and event date." [represented exactly as entered in Issue Report]	
10100114785 ETH.MESH. 02630272-277	March 11, 2010	April 30, 2010	A complaint was received from an affiliate with a customer complaint regarding TVT. It was reported that 810081B was utilised for a patient with sever Stress Urinary incontinence. The tape seemed to be very narrow over the midurethra after insertion. Initially, [REDACTED] thought it had doubled over - but on closer inspection it had narrowed and had started fraying - little bits of polypro falling off everywhere. [REDACTED] assures that over adjusting /tensioning did not occur and has not seen the tape behave in this manner from any previous experience. Completed surgery with the device in question. However was not happy with the quality of the device. [represented exactly as entered in Issue Report]	Not Reportable - Document rationale why not to report: Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point, the clinician may either continue with another device or treatment modality or completely abort the procedure. There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure.

Peggy Pence, PhD, RAC, FRAPS
Expert Witness Report
Ethicon, Inc. Pelvic Repair System,
Products Liability Litigation

Appendix A: Professional Summary

October 14, 2013

Peggy C. Pence, PhD, RAC, FRAPS

Symbion Research International, Inc.
3537 Old Conejo Road, Suite 115, Newbury Park, California 91320
ppence@symbionresearch.com | (805) 214-3714

PROFESSIONAL SUMMARY

Dr. Pence offers over 40 years of experience in the research and development of traditional pharmaceutical and biotechnology-derived therapeutic products and medical devices, including in vitro diagnostics. Dr. Pence began her career at Eli Lilly and Company in 1970 in basic immunology research and later transitioned to clinical development and regulatory affairs. She subsequently held key project and clinical management positions at several emerging-growth companies, namely the U.S. start-up of Serono Laboratories, Triton Biosciences (acquired by Berlex Laboratories, Inc.), and Amgen, Inc. In 1992, Dr. Pence founded a consulting firm that was incorporated in 1995 as Symbion Research International, a full-service contract research organization. She has been President and Chief Executive Officer since that time. Dr. Pence is also Chief Executive Officer of Illuminostics, LLC, which she co-founded in January 2012 for the purpose of providing medical imaging services both for clinical trials and also to aid in the diagnosis and monitoring of disease in medical practice.

Over the course of her longstanding career, Dr. Pence has worked with over 80 companies and over 90 drugs, biologics, and medical devices spanning multiple therapeutic areas. She has broad experience in regulatory affairs and strategic planning, nonclinical testing, and all phases of clinical trials. Dr. Pence has enjoyed success in leading development programs for a number of novel products and has designed and managed numerous clinical studies, from first-in-man to pivotal studies to support marketing applications. She established, staffed, and directed the Clinical Quality Assurance and Document Control department at a leading biotechnology company, Amgen, Inc. She has directed collaborative clinical programs with foreign affiliates to reduce overall clinical development time and costs, and enhance quality and usability of data globally for marketing applications. Dr. Pence has served as the U.S. Agent or authorized representative for FDA (Food and Drug Administration) matters for medical device, pharmaceutical, and biopharmaceutical companies. She has prepared numerous regulatory submissions and consulted with the FDA concerning INDs, NDAs, BLAs, IDEs, 510(k)s, and PMAs. She has guided and coordinated product development activities from process development through marketing plans. Therapeutic areas of experience include neurology, neuropsychology, oncology, hematology, infectious disease, rheumatology, nephrology, respiratory disorders, women's health, metabolic and growth disorders, gastroenterology, burns, wound healing, and ophthalmology.

Among her accomplishments, Dr. Pence has consulted for a multinational pharmaceutical company to develop strategy and implement a global clinical data management system and also for a leading software company to develop information management solutions for the pharmaceutical and biotechnology industries. Dr. Pence has been instrumental in assisting a number of companies (both emerging-growth companies and established industry leaders) to evaluate current operations and implement new processes and procedures to achieve greater efficiency and ensure compliance with current regulations.

Dr. Pence earned her undergraduate degree in Microbiology from Louisiana Tech and her PhD in Toxicology from Indiana University. She is an active industry speaker and educator and has developed and is the instructor for two graduate-level courses for the California State University system: "Clinical Trials and Quality Assurance" and "Clinical Trials Project Management: Managing Clinical Trials." Dr. Pence founded and chaired the Drug Information Association (DIA) Biotechnology Subgroup and chaired 10 consecutive DIA workshops on biotechnology from 1991 through 2001. Dr. Pence holds the U.S. Regulatory Affairs Certification (RAC) designation and has served on the Regulatory Training Course Faculty, DIA, and as an instructor for the Orange Country Regulatory Affairs Discussion Group (OCRA) for candidates for Regulatory Affairs Certification. Dr. Pence is a RAPS (Regulatory Affairs Professionals Society) Fellow (FRAPS), a peer-reviewed credential for which she was selected based on her experience, contributions, and leadership in the regulatory profession. She serves on the Board of Directors or Advisory Board for multiple organizations.

PROFESSIONAL EXPERIENCE

Founder, President and Chief Executive Officer | Symbion Research International, Inc.
Newbury Park, California | 1995-Current

- Responsible for establishing and maintaining corporate culture, ethical standards, and vision.
- Determine corporate direction and oversee business development.
- Responsible for executive decisions regarding systems implementation, policies, and procedures.
- Provide expert advice to clients regarding regulatory, nonclinical, and clinical development matters and product development strategic planning.
- Serve as regulatory liaison with FDA for client companies.
- Provide expert advice and represent clients for FDA meetings.
- Provide guidance to clients to achieve resolution of non-compliance issues identified during FDA inspection.
- Function as director of product development for virtual companies.
- Directly oversee and participate in clients' pivotal development programs (i.e., maintain a "hands-on" approach).
- Provide leadership and counsel to Symbion teams assigned to clients' projects.
- Design clinical protocols and programs, proposing innovative methods as appropriate.
- Organize and chair (as appropriate) multi-center Investigators'/Study Coordinators' Meetings.
- Direct the conduct, management, monitoring, data management, analysis, and reporting of clinical trials.
- Perform critical review of key regulatory submissions to ensure highest quality and successful submissions.
- Evaluate clinical operations of client companies and recommend solutions to increase effectiveness; accordingly, revise and develop Standard Operating Procedures (SOPs).
- Perform quality assurance audits of pivotal clinical trials.
- Conduct training programs in regulatory affairs, Good Clinical Practice, and Good Laboratory Practice.
- Experience with novel therapeutic products, including oncolytic viruses, tissue-engineered products, interferons, monoclonal antibodies, neurotrophic factors, growth factors, peptides, and toxins, as well as new chemical entities; Class I, II, and III medical devices, including in vitro diagnostics; innovative drug delivery systems; and combination products. Clinical indications studied include a variety of cancer types, neurological conditions, pain management, cognitive disorders, diabetes, infectious diseases, including HIV/AIDS and other sexually transmitted diseases, respiratory disorders, gastrointestinal disorders, hepatitis, burns, chronic wounds, and women's health concerns.

Co-Founder and Chief Executive Officer | Illuminostics, LLC
Newbury Park, California | 2012-Current

- Establish and maintain corporate culture, ethical standards, and vision.
- Determine corporate direction and oversee business development.
- Responsible for executive decisions regarding systems implementation, policies, and procedures.
- Provide leadership and counsel to Illuminostics team projects.
- Oversee development and revision of Standard Operating Procedures (SOPs).

President | Product Development Consulting
Newbury Park, California | 1992-1995

- Designed and conducted clinical programs, Phases I to III.
- Established new clinical functions or departments for client companies, including Standard Operating Procedures (SOPs) and systems.

PROFESSIONAL EXPERIENCE (Continued)

- Evaluated, prepared study reports, and summarized nonclinical and clinical data for NDA submission.
- Evaluated and re-engineered product development processes for implementation of new information technology systems, assessing and planning conversion strategy.
- Served as key member of clients' product development teams, providing expert advice on regulatory and product development matters and strategic planning.
- Prepared regulatory submissions (including clinical protocols and amendments; Investigator's Brochures; initial IND submissions, IND amendments and annual reports; 510(k)s, PMAs; Clinical Study Reports, etc.).
- Consulted for a multinational pharmaceutical company to develop strategy and implement a global clinical data management system.
- Provided expert advice to leading software company to develop information management solutions for the pharmaceutical and biotechnology industries.

Amgen, Inc. | Thousand Oaks, California
Associate Director, Clinical Quality Assurance and Document Control
Manager, Clinical Operations
Manager, Clinical Studies
1988-1992

- Key member of product development teams for consensus interferon and wound-healing growth factors.
- Responsible for preparation or critical review of significant parts of IND submissions.
- Designed and directed clinical programs for consensus interferon and "first-time-in-man" studies of recombinant wound-healing growth factors; consensus interferon program led to licensing approval for treatment of hepatitis C virus infection.
- Awarded management responsibility for ongoing gamma interferon clinical programs.
- Established and staffed clinical quality control and assurance department and functions, developed procedures and systems, and achieved major targeted deadline (for human granulocyte colony stimulating factor [G-CSF] program) within first three months of operation.
- Managed staff responsible for adverse event and concomitant medication coding across all clinical programs worldwide.
- Directed the establishment and functioning of a Clinical Records and Information Center for the storage, organization, protection, and management of clinical trial documents across all clinical programs, including an International Records Library.
- Directed the development of a Case Report Form (CRF) tracking system for all clinical programs, including operating procedures and reporting capabilities.
- Developed comprehensive training curriculum for clinical development staff.
- Responsible for developing and administering annual and five-year research and development plans and budgets.
- Managed staff of over 40 clinical research professionals.
- For all functions, met all targeted deadlines and achieved all departmental and divisional goals at a level of 125% to greater than 150%.

Manager, Therapeutics Projects | Triton Biosciences, Inc.
Alameda, California | 1986-1988

- Project manager accountable for all planning, direction, scheduling, monitoring and control of assigned projects, including recombinant interferon-beta and transforming growth factor, from process development through marketing plans.
- Organized and chaired formal project reviews with co-development company and also internal project team; provided company officers with regular progress reports, through both written documents and oral briefings.

PROFESSIONAL EXPERIENCE (Continued)

- Prepared master plan for development of a new purification procedure and formulation; assured project control and adherence to the plan to achieve target date for completion.
- Directed compilation from three separate databases and writing of clinical safety assessment for over 500 patients for FDA submission.
- Responsible for evaluation of therapeutic and commercial potential of new chemical entity.
- Key member of strategy-setting team for therapeutic projects.
- Managed major extramural nonclinical research programs; designed and implemented nonclinical toxicology, pharmacology, and efficacy studies.

Pharmaceutical Research Manager | Serono Laboratories, Inc.
Randolph, Massachusetts | 1983-1986

- Responsible for the design and execution of nonclinical and clinical development programs in two major product areas: interferon-beta and human growth hormone, both native and recombinant.
- Awarded management responsibility for ongoing trials of bovine thymus peptide product (thymostimulin) in AIDS and AIDS-Related Complex (ARC) patients.
- Took over a mismanaged trial, cleaned it up, and administered FDA's inspections of this trial (including both sponsor and investigator) to successful outcomes.
- Successfully designed and completed Phase I trial, inspected by FDA subsequent to above-noted inspections; inspection completed in approximately two hours, resulting in inspector's pronouncement that this was one of the best audit results he had seen.
- Directed development of collaborative clinical programs with foreign affiliates, notably the United Kingdom, France, Israel, and Italy, to reduce corporate's overall clinical development costs and enhance quality and usability of data globally for marketing applications.
- Designed and implemented four Phase I and II trials, designed and developed Phase III multi-center trials in six indications, including ocular and sexually-transmitted infectious diseases, cervical intraepithelial neoplasia, and growth hormone deficiency. Organized and chaired four multi-center Investigators'/Study Coordinators' Meetings.
- Conceived and successfully proposed Phase III clinical strategy to FDA to reduce the time to NDA submission by approximately one year.
- Recommended a clinical study that led to an application for use patent.
- Implemented a clinical study in collaboration with the National Institutes of Health, which was applauded as a potential landmark study and eventuated letters of commendation both from senior company management and the study investigators.
- Collaborated with overseas manufacturing facilities (Israeli, Italian, and Swiss affiliates) to develop task completion schedules and resolve process development issues; personally arranged characterization and validation studies and coordinated activities with affiliate and contract laboratories to assure timely completion.
- FDA liaison (telephone contacts, formal presentations and meetings).
- Prepared Supplemental New Drug Application and subsequently prepared a presentation of the data therein for FDA Advisory Committee meeting, at FDA's invitation.
- Wrote protocol and SOPs for enzyme-linked immunosorbent assay to detect antibody development in patients treated with interferon-beta.
- Coordinated validation of an antibody assay (for human growth hormone patients) by diagnostics affiliate to effect a 50% savings in assay costs compared to extramural laboratory charges.
- Prepared summary of all non-U.S. safety data (interferon-beta) for submission to regulatory agencies in support of marketing applications; recognized by corporate and affiliate offices for value of contribution.
- Directed the activities of four clinical research professionals and two secretaries.

PROFESSIONAL EXPERIENCE (Continued)

Eli Lilly and Company | Indianapolis, Indiana
Medical Information Administrator, Regulatory Affairs
1982-1983
Educational Leave of Absence to Complete Doctoral Research
1980-1982
Cosmetic Chemist, Research and Development | Elizabeth Arden Division
1974-1977
Associate Microbiologist, Immunology Research Laboratory
1970-1974

- Broad exposure to the planning, drug development, and decision-making processes at a leading pharmaceutical corporation.
- Responsible for monitoring Phase III and IV clinical trials for original and supplemental NDA submissions.
- Contributed to preparation of clinical protocols, CRFs, and Investigator's Brochures.
- Collaborated with biostatisticians, computer programmers, and data analysts to establish data entry and verifications systems.
- Prepared a variety of regulatory submissions, including quarterly reports to the newly approved NDA for Humulin®, the first product of recombinant DNA origin to be approved for sale.
- Acquired experience in multiple product categories: antiemetic, narcotic analgesic, anti-inflammatory, and antiparkinsonism drugs.
- Supervised staff of three non-exempt personnel.
- As cosmetic chemist, developed complete line of powder products, troubleshot for pilot plant and production, worked closely with marketing and claims substantiation departments; conducted skin physiology research.
- As associate microbiologist, participated in the design and execution of *in vivo* and *in vitro* experiments to develop a reliable and reproducible screening assay for identifying agents affecting cell-mediated immunity; acquired tissue culture and laboratory animal experience.

EDUCATION

Doctor of Philosophy (PhD), Toxicology, Pharmacology minor
Indiana University (Medical School campus) | Indianapolis, Indiana | 1983
Thesis: Comparative effects of cannabinoids alone and in combination with other centrally acting drugs.
Doctoral research conducted at the Eli Lilly Laboratory for Clinical Research (Indianapolis, Indiana):

- Planned and personally executed all aspects of three clinical pharmacology and toxicology studies, from protocol conception to subject selection to Clinical Study Report.
- Synthetic cannabinoid Cesamet® studied in two of these trials approved by FDA, December 1985; prepared report on drug abuse liability trial results for FDA Drug Abuse Advisory Committee, which report was central to Committee's recommendation (1983) for scheduling under the Controlled Substances Act.

Bachelor of Science (BS), *Magna cum Laude,* Microbiology
Louisiana Polytechnic University (Louisiana Tech) | Ruston, Louisiana | 1969

ACADEMIC HONORS

2008	Selected for Bossier High School Alumni Hall of Fame | Bossier City, Louisiana
1982	Member of Sigma Xi, The Scientific Research Society
1982	Third place, annual Sigma Xi competition for graduate research presentations | Indiana University School of Medicine
1981	Second place, annual Sigma Xi competition for graduate research presentations | Indiana University School of Medicine
1966	Valedictorian, Bossier High School | Bossier City, Louisiana

PROFESSIONAL CERTIFICATION OR DESIGNATION

- U.S. Regulatory Affairs Certification (RAC)
- Regulatory Affairs Professionals Society Fellow (FRAPS) | 2009

CURRENT PROFESSIONAL MEMBERSHIPS

- Regulatory Affairs Professionals Society (RAPS)
- The Food & Drug Law Institute (FDLI, corporate membership)
- Drug Information Association (DIA)
- International Society for Pharmacoepidemiology (ISPE)
- Southern California Biomedical Council (SoCalBio, corporate membership)
- Orange County Regulatory Affairs Discussion Group (OCRA)

SELECTED HONORS AND AWARDS

October 6, 2010	OCRA and San Diego Regulatory Affairs Network (SDRAN) Certificate of Appreciation for Presentation: "Getting Your Product to Market in the New Regulatory Environment," San Diego, California
June 17, 2010	OCRA Certificate of Appreciation for Dedication to OCRA, Irvine, California
June 16-17, 2010	OCRA Certificate of Appreciation: Speaker (Moderator), 13th Annual FDA-OCRA Educational Conference, "The Business of Compliance," Irvine, California
August 1, 2009	OCRA Certificate of Appreciation: US RAC Study Group Presenter, Brea, California
June 9-10, 2009	OCRA Certification of Appreciation: Award Recipient, OCRA Volunteer Appreciation 2009 for Support of OCRA, Irvine, California
November 19, 2008	OCRA Certificate of Appreciation: Global Clinical Trials, Carlsbad, California
September 6, 2008	OCRA Certificate of Appreciation: US RAC Study Group Presenter, Brea, California

ACADEMIC APPOINTMENTS

2012-2013	Developed Course and Instructor, California State University, Fullerton, Biology 538: Clinical Trials Project Management: Managing Clinical Trials
2011-present	Developed Course and Part-time Faculty Member, California State University, Channel Islands, Biology 516: Clinical Trials and Quality Assurance

ACADEMIC APPOINTMENTS (Continued)

Spring 2009	Instructor/Advisor, California State University, Channel Islands, Master of Science in Biotechnology Program Team Projects, Subject: Development Pathway and Issues for Probiotics as Therapeutics

BOARDS OF DIRECTORS AND ADVISORY BOARDS

2012 - present	The Food and Drug Law Institute (FDLI), *Update* Editorial Advisory Board
2009 - 2013	Biotechnology and Health Programs Advisory Board, California State University, Channel Islands
2009	Clinical Trials Certificate Program Advisory Board, California State University Program for Education and Research in Biotechnology (CSUPERB)
2008 - 2009	Biotechnology Advisory Committee, California State University, Channel Islands
2007 - present	Board of Directors, CompassioNow (formerly CareNow Foundation)
2006 – 2008	Scientific Advisory Board, CytoDyn, Inc.
2003 – 2005	Board of Directors, CytoDyn, Inc.
2003	Board of Directors, VCBio
1989-present	Board of Directors, The Iraida Foundation
1987	First Editorial Advisory Board, *BioPharm Manufacturing*

SELECTED PROFESSIONAL CONTRIBUTIONS

September 24, 2013	"Quality Executive Leadership Series: FDA and Industry Executives Working Together to Improve Quality," Workshop between U.S. Food and Drug Administration and Industry Executives, Irvine, California
2009	Southern California Biomedical Council (SCBC) Gold Coast Event Planning Committee
2009	Co-Founder & Meetings Chairperson, Venture Coast Life Science Innovators (VCLSI)
1994 - 1996	Drug Information Association (DIA) Annual Meeting Program Committee, Biotechnology Track - *Session Chairperson: Current Research Targets in Biotechnology Including Therapeutics and Therapeutic Vaccines, 1995*
1994	DIA Regional Steering Committee
1993 - 1995	DIA Steering Committee of the Americas
1990's	Originator and Chair, Drug Information Association (DIA) Biotechnology Subgroup

PUBLICATIONS

- Robson MC, Phillips LG, Thomason A, Altrock BW, Pence PC, Heggers JP, Johnston AF, et al. "Recombinant human platelet-derived growth factor-BB for the treatment of chronic pressure ulcers." Ann Plast Surg 1992; 29: 193-201.
- Lemberger L, Rubin A, Wolen R, DeSante K, Rowe H, Forney R, Pence P. "Pharmacokinetics, metabolism and drug-abuse potential of nabilone." Cancer Treatment Reviews 1982; 9 (Supplement B): 17-23.

CONFERENCE CHAIRMANSHIPS

February 12-13, 2001	9th Annual Drug Information Association (DIA) Workshop, Program Co-Chairperson, "Biotechnology: Global Perspectives," Dana Point, California
May 6-7, 2000	8th Annual DIA Biotechnology Workshop, Program Co-Chairperson, "Biotechnology: Global Perspectives," Dana Point, California - *Session Chairperson: "Biotechnology in Australia, Europe, and Japan"*
February 1-2, 1999	DIA 7th Annual Biotechnology Workshop, Program Chairperson, "Biotechnology: Product Development for the New Millennium," Dana Point, California
February 5-6, 1998	DIA 6th Annual Biotechnology Workshop, Program Chairperson, "Clinical Trials and Product Development in Biotechnology," Dana Point, California - *Session Co-Chairperson: "Getting into the Clinic with Novel Products – DNA Vaccines and Gene Therapy"*
February 20-21, 1997	DIA 5th Annual Biotechnology Workshop, Program Chairperson, "Clinical Trials in Biotechnology," Dana Point, California
January 29-30, 1996	DIA 4th Annual Biotechnology Meeting, Program Co-Chairperson, "Regulatory Reform: Its Impact on Clinical Trials and Product Development in Biotechnology," Newport Beach, California - *Session Chairperson: "Key Considerations for Regulatory/Clinical Development in the Current Industry Environment"* - *Speaker: "Perspectives on the ICH GCP Guideline"*
January 30-31, 1995	DIA 3rd Annual Biotechnology Meeting, Program Co-Chairperson, "Clinical Trials in Biotechnology," Newport Beach, California - *Session Chairperson: "Optimizing Data Management for Emerging Biopharmaceutical Companies"*
June 6-7, 1994	DIA Annual Meeting, Biotechnology Track Co-Chairperson
January 30-February 1, 1994	DIA Annual Symposium on Biologics and Biotechnology, Program Co-Chairperson, "Clinical Trials in Biotechnology: Planning to Prevent the Pitfalls," Newport Beach, California - *Session Chairperson: "Tactics for Execution"* - *Speaker: "Performing with the Best Actors: Efficiency and Quality"*
May 19-21, 1993	DIA Biotechnology Workshop, Program Chairperson, "Biotechnology: Meeting the Challenges of the 1990s," Boston, Massachusetts - *Speaker: "Integrating CAPLAR/CANDA in the Product Development Process"*
November 20-22, 1991	DIA Biotechnology Workshop, Program Chairperson, "Clinical Development of Biotechnology Products," Santa Monica, California - *Speaker: "A Comprehensive Approach to Achieving Efficiency and Quality in Clinical Research"*

SPONSORED SYMPOSIA

October 14, 2008	PQC Consulting, Inc., and Symbion Research International, Inc., Co-Sponsored Symposium, "Good Clinical Practice and the Clinical Study Process," Lead Instructor: Peggy Pence, PhD, RAC, Los Angeles, California
October 15, 2003	Symbion Research International, Inc., and Interface International Consultancy, Ltd., Co-Sponsored Symposium: "How to CE Mark a Medical Device," Instructor: Brian James, PhD, FBIRA

SPONSORED SYMPOSIA (Continued)

November 5, 2002	Symbion Research International, Inc., and Interface International Consultancy, Ltd., Co-Sponsored Symposium: "European Regulations: Medical Devices, Drug-Device Combinations, Orphan Drugs and a Glance into the Future," Instructor: Brian James, PhD, FBIRA, La Jolla, California
November 4, 2002	Symbion Research International, Inc., and Interface International Consultancy, Ltd., Co-Sponsored Symposia: "Drug-Device Combinations: A European Perspective" and "European Regulations: A Glance into the Future," Instructor: Brian James, PhD, FBIRA, Irvine, California

SELECTED PRESENTATIONS

October 1, 2013	"The Importance of Ethics - Postmarketing Challenges," Situation Room Speaker, 2013 RAPS Annual Conference: The Regulatory Convergence, Boston, Massachusetts
September 30, 2013	"The Importance of Ethics - Premarketing Challenges," Situation Room Speaker, 2013 RAPS Annual Conference: The Regulatory Convergence, Boston, Massachusetts
August 1, 2009	"Medical Device Submissions and Post-Approval Requirements for Medical Devices," Instructor for OCRA, US Regulatory Affairs Certification (RAC) Study Group
February 26, 2009	"Finding New Medical Therapies: The R&D Process – Discovery Research through Post-Marketing," Guest Lecturer: Biology 601, Master of Science in Biotechnology program, California State University, Channel Islands
November 19, 2008	"The Use of Databases and Electronic Data Capture in Clinical Studies," Speaker (Co-Presenter with Diane Ascoli) and Panel Member: OCRA - San Diego Regulatory Affairs Network (SDRAN) Joint Meeting, "Global Clinical Trials: An Overview and Update," Carlsbad, California
September 6, 2008	"Device Submissions: PMA, 510(k) (21 CFR Regulations: Devices - 807, 809 & 814)," Instructor for OCRA, US Regulatory Affairs Certification (RAC) Study Group
June 10, 2008	"Drugs/Biologics Product Development: Understanding the Complexities, Managing the Risks," Guest Lecturer: Biology 601, Master of Science in Biotechnology program, California State University, Channel Islands
March 27, 2008	"Personalized Medicine, Regulatory Perspective," Speaker and Panel Member: Southern California Biomedical Council (SoCalBio) Networking Forum: "Personalized Medicine Are We There Yet," Westwood, California
April 24, 2007	"Successful Product Submissions," (Interactive) Audio Conference: Thompson Publishing Group, Co-Presenter with Dr. Kathryn Kimmel
April 17, 2007	"Clinical Data Management: Annual Good Clinical Practices Review," Corporate Program, San Diego, California
November 15, 2006	"Risk-Benefit Analysis in Clinical Development," BioFlorida Annual Conference, Gainesville, Florida
June 6, 2006	"Clinical Data Management: Case Report Form Fundamentals," Corporate Program, San Diego, California
March 2, 2006	"Clinical Data Management: Annual Good Clinical Practice (GCP) Training Workshop," Corporate Program, San Diego, California
November 8, 2005	"Navigating the Drug Development Pipeline from Innovation to Market," Presentation to the Women in Health Administration of Southern California
May 20, 2004	"Integrating Regulatory, Clinical and Marketing Efforts into a Profitable Reimbursement Strategy," Audioconference: FDA News, Co-Presenter with Jennifer Murray and Chris Waugh
October 28, 2003	"Good Clinical Practice (GCP) and Regulatory Training Workshop," Corporate Program, Westlake Village, California
October 20, 2003	"Safari of Life, My Personal Journey: Bench to Business," Presentation to Forum for Women Entrepreneurs, San Diego, California

SELECTED PRESENTATIONS (Continued)

June 24, 2003	"Good Clinical Practice (GCP) and Regulatory Training Workshop," Corporate Program, Westlake Village, California
December 1-3, 1993	Drug Information Association (DIA) Pharmaceutical Document Management, Program Speaker, San Francisco, California
September 1, 1993	"Good Clinical Practices and Effective Study Monitoring Workshop," Corporate Program, San Diego, California
September 23, 1992	"The Oracle Biotechnology Seminar: Flexible Information Management Within A Regulated Industry," An Executive Seminar with Dr. Peggy Pence, Oracle Corporation, Santa Clara, California

SELECTED CONTINUING EDUCATION

September 30-October 2, 2013	2013 Regulatory Affairs Professionals Society (RAPS) Annual Conference: "The Regulatory Convergence," Boston, Massachusetts
June 6, 2013	"Skadden Seminar for Pharmaceutical, Biotechnology and Medical Device Companies: A Dialogue on Regulation, Litigation and Shareholder Activism," Costa Mesa, California
November 1, 2012	"RAPS/FDA Case for Quality Forum," Irvine, California
April 24-25, 2012	The Food and Drug Law Institute's 55th Annual Conference, Washington, D.C.
November 2, 2011	"How to Avoid the Escalation of Enforcement Activities," Orange County Regulatory Affairs Discussion Group (OCRA), Irvine, California
October 19, 2011	"Corporate Compliance: Understanding the Current Enforcement Climate," OCRA and San Diego Regulatory Affairs Network (SDRAN) Joint Meeting, San Diego, California
September 26-27, 2011	The Food and Drug Law Institute's Advertising and Promotion Conference for the Pharmaceutical, Medical Device, Biologic and Veterinary Medicine Industries, Washington, D.C.
February 8-10, 2011	Medical Design and Manufacturing (MD&M) West 2011 Conference, Anaheim, California
October 7, 2010	Town Hall Meeting, FDA's Center for Devices and Radiological Health (CDRH), Irvine, California
October 6, 2010	"Getting Your Product to Market in the New Regulatory Environment," OCRA and SDRAN Joint Meeting, San Diego, California
June 16-17, 2010	"The Business of Compliance," 13th Annual FDA-OCRA Educational Conference, Irvine, California - *Session Moderator: "Enforcement Activities of Significance"*
May 19, 2010	California Life Sciences Day at the State Capitol, Sacramento, California
April 28, 2010	"Risk Management for Regulated Industries," OCRA, Irvine, California
March 10, 2010	"Navigating CAPA: Smooth Sailing with Continuous Improvement," OCRA, Irvine, California
February 8-10, 2010	"Marketing a Medical Device in the US" and "The Future is Now: Anticipating a New Era of FDA Enforcement, Parts I & II," MD&M West 2010 Conference, Anaheim, California
January 26, 2010	"Regulatory Strategies for Biologics Development," SDRAN Annual Meeting & Presentation, San Diego, California
November 19, 2009	"Adoption Process of Novel Technologies: Challenges and Solutions," Drug Safety Executive Council (DSEC) Webinar
November 6, 2009	"Convergence, Creating BioSynergy," BioFlorida's 12th Annual Conference, Orlando, Florida
October 21, 2009	"European Regulation on Advanced Therapies," The Weinberg Group, Webinar
September 30, 2009	"ANDA vs. 505(b)(2) – When and Why?," The Weinberg Group, Webinar

SELECTED CONTINUING EDUCATION (Continued)

September 14-16, 2009	Regulatory Affairs Professionals Society (RAPS) Annual Conference & Exhibition, Philadelphia, Pennsylvania
September 9, 2009	"FDA's New Strategy on Enforcement: The Growing Perils of Inadequate Compliance," The Weinberg Group, Webinar
June 9-10, 2009	"The Challenges of Ensuring Product Safety," 12th Annual FDA-OCRA Educational Conference, Irvine, California
May 27, 2009	"Global Lessons in Developing Biosimilars," The Weinberg Group, Webinar
April 15, 2009	"Pharmaceutical Development in Europe: Key Points to Consider," The Weinberg Group, Webinar
April 7-8, 2009	2009 Florida Medical Device Symposium, Florida Medical Manufacturer's Consortium, Inc., Tampa, Florida
January 29, 2009	"Workshop on Accessing Government Funding for Bioscience Research," Southern California Biomedical Council (SoCalBio), Westwood, California
November 19, 2008	"Global Clinical Trials: An Overview and Update," OCRA-SDRAN Joint Meeting, Carlsbad, California
September 19, 2008	10th Southern California Biomedical Council Investor Conference, Los Angeles, California
June 16, 2008	Israel Life Sciences Day at BIO 2008, La Jolla, California
June 11-12, 2008	"Regulatory Affairs: Expanding to Global Horizons," 11th Annual FDA-OCRA Educational Conference, Irvine, California
February 8, 2008	"Striving for Regulatory Success in a Changing Environment," Hyman, Phelps & McNamara, PC, Medical Device Seminar, Newport Beach, California
June 11-12, 2007	"Celebrating 10 Years of Regulatory Affairs Education," 10th Annual FDA-OCRA Educational Conference, Irvine, California
November 30-December 1, 2006	2006 Global Summit on AIDS and the Church: Race Against Time, Saddleback Church Campus, Lake Forest, California
November 14-15, 2006	"Intersections: Converging Fields, Emerging Opportunities," BioFlorida Annual Conference, Gainesville, Florida
August 13-18, 2006	XVI International AIDS Conference, Toronto, Canada
November 29-30, 2005	HIV/AIDS Conference, Saddleback Church Campus, Lake Forest, California
June 4-5, 2003	"Understanding the Changing Landscape," 6th Annual FDA-OCRA Educational Conference, Irvine, California
March 12-13, 2001	"Opportunities for Drug Development and Discovery in Women's Health," Drug Information Association (DIA), Washington, D.C.
October 25, 1999	"Annual Update on Women's Health Research: Discoveries and Implications," Ninth Annual Scientific Advisory Meeting, Society for the Advancement of Women's Health Research, Washington, D.C.
March 22-23, 1999	"Contracting with Site Management Organizations," Barnett International Conference Group, Philadelphia, Pennsylvania
June 25-29, 1995	"The Changing Regulatory Environment and Its Impact on Global Healthcare," DIA 31st Annual Meeting, Orlando, Florida
May 20-25, 1995	Ninth BIO International Biotechnology Meeting & Exhibition, San Francisco, California
December 7-8, 1993	"In Vitro Diagnostics – A Regulatory Update," Regulatory Affairs Professionals Society (RAPS) 1993 Educational Programs, San Francisco, California
July 11-15, 1993	"Global Drug Development: Focus on the Americas," DIA 29th Annual Meeting, Chicago, Illinois
April 12-16, 1993	Association of Biotechnology Companies 7th International Biotechnology Meeting & Exhibition, Research Triangle Park, North Carolina

SELECTED CONTINUING EDUCATION (Continued)

June 8-11, 1992	"Pharmaceutical Development: National and Transnational Dynamics," Drug Information Association, San Diego, California
February 27, 1992	"Micro Planner X-Pert" Training, Amgen Corporate Information Technologies, Thousand Oaks, California
Circa 4th Quarter 1991	"Preparing for an FDA-GCP Audit," Barnett International Seminar, prepared and presented for Amgen, Inc.
January 10-14, 1990	"Clinical and Experimental Approaches to Dermal and Epidermal Repair: Normal & Chronic Wounds," 3rd International Symposium on Tissue Repair, Miami, Florida
May 18-20, 1988	"Project Management in the Pharmaceutical Industry," The Institute for Applied Pharmaceutical Sciences, Los Angeles, California
January 16-17, 1986	"Introduction to Laboratory Techniques: Biochemical Separations," Cook College, Continuing Professional Education, Rutgers University, New Brunswick, New Jersey
November 14-15, 1985	"Gene and Its Product," Cook College, Office of Short Courses and Professional Training, Rutgers University, New Brunswick, New Jersey
July 11, 1984	"Ophthalmic Toxicology," The Center for Professional Advancement, East Brunswick, New Jersey

SELECTED COMMUNITY AND CIVIC ACTIVITIES

2012	Charter Member, Rotary E-Club of One World
2006 – 2011	Rotary International, The Rotary Club of Westlake Village - *International Committee and Meals on Wheels Administrator, 2008* - *Program Chair, 2009 – 2010* - *Club Service Chair and Board of Directors, 2010 – 2011*
2002	Ageless for Life Radio Show, Health and Fitness Speaker and Consultant, Chicago, Illinois
2001 – 2002	Los Angeles World Affairs Council, International Circle
1983	Instructor, City/County Marijuana Education Program, Indianapolis, Indiana
1983	Senior Editor and Pharmacology Consultant, Health Alert Publishing Company, Indianapolis, Indiana
1982 – 1984	Invited Speaker on substance abuse, to a variety of parent, student, and professional groups
1982 – 1983	Volunteer Staff by Invitation, Fairbanks Hospital, specializing in the treatment of alcoholism and drug addiction, Indianapolis, Indiana

Peggy Pence, PhD, RAC, FRAPS
Expert Witness Report
Ethicon, Inc. Pelvic Repair System,
Products Liability Litigation

Appendix B: List of Items Provided or Identified for Review

October 14, 2013

Dr. Peggy Pence PhD, RAC, RAPS Fellow
Expert Witness Report – Appendix B
List of Items Provided or Identified for Review

I. 510(k) Summaries		
K Number	**Product Title**	**Website**
K001122	PROLENE Soft (Polypropylene) Mesh	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k001122
K001625	Pronova Nonabsorbale suture	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k001625
K012628	TVT System with three accessories (modification)	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k012628
K013718	Gynemesh PROLENE Soft (Polypropylene) Mesh	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k013718
K033568	Gynecare TVT Obturator Device	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k033568
K052401	Gynecare TVT Secur System	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k052401
K100485	Gynecare TVT Exact Continence System	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k100485
K100936	Gynecare TVT Abbrevo Continence System	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k100936
K132054	Gynecare TVT Exact Continence System	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k132054
K915774	PROLENE Polypropylene Mesh Plug W/ onlay patch	FDA 510(k) Searchable Database: K962530 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k915774

I. 510(k) Summaries (Continued)		
K962530	Modified PROLENE Polypropylene mesh nonabsorbable synthetic surgical mesh	FDA 510(k) Searchable Database: K001122 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k962530
K963226	ProteGen Sling (Cleared under device name "Surgical Fabrics")	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k963226
K972412	PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k972412
K974098	Gynecare TVT Tension-free Vaginal Tape	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k974098
K984220	Modification: PROLENE (Polypropylene) Hernia System	FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn_template.cfm?id=k984220

II. Depositions	
Deponent	**Date**
Axel Arnaud, MD	July 19-20, 2013
Boris Batke	August 1-2, 2013
Catherine Beath	July 11-12, 2013
Christophe Vailhe, PhD	June 20-21, 2013
Daniel Burkley, MS	May 22-23, 2013
Daniel Lamont	September 11, 2013
Daniel Smith	May 15-16, 2013
Daniel Smith	June 4-5, 2013
David Robinson, MD	July 24-25, 2013
David Robinson, MD (ROUGH)	September 11, 2013
Greg Jones	August 20, 2013
Joerg Holste DVM, PhD	July 29-30, 2013
Laura Angelini	September 16, 2013
Martin Weisberg, MD	May 30-31, 2013
Martin Weisberg, MD	August 9, 2013
Piet Hinoul, MD, PhD	June 26-27, 2013
Susan Lin	May 2-3, 2013
Thomas Barbolt, BS, PhD	August 14, 2013

III. Devices
Gynecare TVT Laser Tension-Free Support for Incontinence
Gynecare TVT-Obturator System Tension Free Support for Incontinence

IV. Exhibits

IV. a. Axel Arnaud Exhibits

Exhibit #	Date	Description	Bates #
T-832	September 2, 2008	Email Re: Demande info – historique TVT	ETH.MESH.03932905
T-833		The history of TVT	ETH.MESH.03932912-14
T-834		Curriculum Vitae of Axel Arnaud MD	
T-835	February 20, 2003	Email Re: TVT Complications (an Prof. Hausler)	ETH.MESH.03911107-08
T-836	July 21, 2004	Email Re: TVT Erosion?	ETH.MESH.03910799-800
T-837	January 2003	Hilton P, et al Postural Perineal pain associated with perforation of the lower urinary tract due to insertion of a tension-free vaginal tape BJOG 2003;110:79-82	
T-838	September 2001	Wyczolkowski M, et al Reoperation after complicated tension-free vaginal tape procedures The Journal of Urology 2001;166:1004-1005	
T-839	November 28, 1999	Email Re: TVT event	ETH.MESH.03917309-12
T-840	January 31, 2006	Emails Re: TVT – TVT-O Specifications	ETH.MESH.03911712-15
T-841	June 6, 2003	Email Re: TVT Serious complication	ETH.MESH.03907853-54
T-842		History of TVT-O	ETH.MESH.03932909-11
T-843		Second Generation TVT	ETH.MESH.03907468-69
T-844		Trans-obturator TVT – Procedure In-Out Pr J. de LEVAL (University of Leige, BELGIUM)	ETH.MESH.03907327-30
T-845	May 25, 2003	Email Re: Follow up Mulberry	ETH.MESH.03910890-92
T-846	June 9, 2003	Email Re: Mulberry stage gate action item closed	ETH.MESH.00261584
T-847	August 14, 2003	Email Re: Transient leg pain with MULBERRY	ETH.MESH.03911390-94
T-848	January 7, 2009	Emil Re: My revised writeup of the DeLeval and Waltrengy visit	ETH.MESH.01202101-03
T-849	February 20, 2006	Email Re: PR Cosson	ETH.MESH.03938897-98

IV. a. Axel Arnaud Exhibits (Continued)			
T-850	March 26, 2003	Email Re: Mulberry	ETH.MESH.883919404-05
T-851	June 2, 2003	Email Re: My noteds from the Thusday evening presentation 5/22/03 and Friday's surgery	ETH.MESH.88862727-28
T-852	June 1, 2009	Email Re: Sample medio TVT-O	ETH.MESH.0860142-44
T-853	2005	Instructions for Use (IFU): Gynecare TVT SECUR System Tension-free Support for Incontinence	ETH.MESH.2340568-90
T-854		Exhibit was not marked at deposition	
T-855	November 30, 2006	Email Re: The more procedure the more problems	ETH.MESH.3921612
T-856	December 5, 2006	Email Re: TVT-SECUR follow up on conference call last week	ETH.MESH.3921580-83
T-857	December 15, 2006	Email Re: TVT-S Cookooks	ETH.MESH.1770534
T-858		TVT-Secur: "Hammocjk" position	ETH.MESH.1770535-40
T-859		TVT-Secur: "U" Position	ETH.MESH.1770541-46
T-860	December 19, 2006	Email Re: TVT-S Cookooks	ETH.MESH.1000731, 34-35
T-861	December 19, 2006	Emails re: TVT-S Cookooks	ETH.MESH.0519476-81
T-862	December 19, 2006	Email Re: TVT Secur	ETH.MESH.3921499-500
T-863	December 20, 2006	Email Re: TVT0-S Cookbooks	ETH.MESH.1784428-35
T-864	January 8, 2007	Email Re TVT Cookbooks	ETH.MESH.3912639
T-865		Both, instructions, with track changes shown	ETH.MESH.3912647-51
T-866	January 9, 2007	Email Re: Report from Austria	ETH.MESH.4204341-42
T-867	December 2006	WOMEN'S HEALTH – Monthly Report December 06	ETH.MESH.4204343
T-868	January 10, 2007	Email Re: Report from Austria	ETH.MESH.3922966-67
T-869	January 16, 2007	Email Re: TVT SECUR Procedural steps	ETH.MESH.3922950-51
T-870	March 9, 2007	Email Re: DRAFT of the latest "cookbook" after my trip to Germany	ETH.MESH.1000323-29
T-871		GYNECARE TVT SECUR System: Key Technical Points (Procedural Pearls)	ETH.MESH.1000449-57

IV. a. Axel Arnaud Exhibits (Continued)			
T-872	May 4, 2007	GYNECARE TVT SECUR System: Key Technical Points	ETH.MESH.0163952-60
T-873	May 22, 2007	Email Re: TVT SECUR EU Experts meeting – feedback & future actions` ETH.MESH.0527832-36	
T-874		Continence Health European Experts Meeting, PowerPoint presentation	
T-875	2006	Marketing Material: No bigger than your palm. No less than a revolution.	ETH.MESH.0158289-93
T-876	January 16, 2007	Email Re: French data on TVT Secur	ETH.MESH.3922953
T-877	June 6, 2007	Email Re: TVT Secur and NICE	ETH.MESH.3922405-06
T-878	October 3, 2007	Email Re: AMS Mini arc	ETH.MESH.3922261
T-879	1996	Ulmsten U, et al An Ambulatory Surgical procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence Int Urogynecol J 1996;7:81-86	ETH.MESH.5795664-69
T-880		License and Supply Agreement	ETH.MESH.088696085-134
T-881	November 15, 1999	Asset Purchase Agreement	ETH.MESH.5972834-66
T-882	November 12, 1999	Consulting Agreement	ETH.MESH.8692673-96
T-883	October 17, 1997	Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure Clinical Report, M. Eriksson (MEDSCAND)	ETH.MESH.8476335-42
T-884	1998	Ulmsten U, et al A Multicenter Study of Tension-Free Vaginal Tape (TVT) for Surgical treatment of Stress Urinary Incontinence Iny Urogynecol J 1998;9:210-213	ETH.MESH.0145085-88
T-885	2001	Nilsson CG, et al Long-term results of the Tension-Free Vaginal Tape (TVT))Procedure for Surgical treatment of Female stress Urinary Incontinence Int Urogynecol J 2001;Suppl 2:S5-S8	ETH.MESH.0658807-10

IV. a. Axel Arnaud Exhibits (Continued)			
T-886	December 2004	Nilsson CG, et al Seven-Year Follow-Up of the Tension-Free vaginal Tape Procedure for Treatment of Urinary Incontinence Obstetrics & Gynecology 2004;104(6):1259-1262	ETH.MESH.3930120-23
T-887	2008	Nilsson CG, et al Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence Int Urogynecol J 2008;19:1043-1047	ETH.MESH.0355003-07
T-888	February 2002	Marketing Material: Gynecare TVT Tension-free Support for Incontinence 5 Years of Proven Performance	ETH.MESH.0339437-42
IV. b. Boris Batke Exhibits			
Exhibit #	**Date**	**Description**	**Bates #**
T-1226		CV of Boris Batke	ETH.MESH.05479501-02
T-1227	July 20, 2007	Email Re: Defining light weight mesh	ETH.MESH.05920616-17
T-1228		Meshes/Devices Chart	
T-1229		Hernia Mesh Development and Incontinence (TVT) Development Timeline	ETH.MESH.1816988-90
T-1230		Chart of different slings and mesh pore size	ETH.MESH.0547953-no Bates numbers
T-1231	March 1-13, 2006	Emails Re: Mesh and Tissue Contraction in Animal	ETH.MESH.05446127-39
T-1232	2005	Klosterhalfen B, et al. "The lightweight and large porous mesh concept for hernia repair." Expert Rev Med. Devices 2005;2(1):1-15	
T-1233	March 2011	Ethicon Polypropylene Mesh Technology, PowerPoint presentation	
T-1234	April 17, 2003	Email Re: Literature list Lightweight Meshes	ETH.MESH.05920530-32
T-1235	February 11-12, 2008	Emails Re: Dr. Schumpelick, with Worldwide "Lightweight" Mesh Strategy Overview PowerPoint presentation attached	ETH.MESH.05920618-28
T-1236	February 29-March 1, 2012	Emails Re: AGES Pelvic Floor conference – Gala Dinner Invitation	ETH.MESH.04015102-04

IV. b. Boris Batke Exhibits (Continued)			
T-1237	June 30, 2003	Ultrapro (Project Edelweiss), PowerPoint presentation	ETH.MESH.05585033-53
T-1238		Chronic Pain: Prevention/future – Bioengineer's point of view, PowerPoint presentation	ETH.MESH.05916450-no Bates numbers
T-1239		Innovations in Mesh Development, PowerPoint presentation	ETH.MESH.04037600-no Bates numbers
T-1240		The (clinical) argument of lightweight mesh in abdominal surgery, PowerPoint presentation	ETH.MESH.0547941-no Bates numbers
T-1241	May 4, 2004	Email Re: Marlex Experience	ETH.MESH.05918776
T-1242		The benefits of Lightweight Meshes in Ventral Hernia Repair (Compilation of Findings for the Well-Informed Surgeon) DVD	
T-1243		Unlabeled flash drive	
T-1244	June 20, 2002	Flexible Implant Chart (in German)	
T-1245	July 19, 2012	Translation of German Flexible Implant Chart	
T-1246	June 1, 2010	Various abstracts from The Journal of Urology 2010;183(4) Supplement:e686	
T-1247	January 13, 2005	Report: Analysis of Competitors meshes: Dynamesh, Dynamesh light, Dynamesh IPOM	ETH.MESH.04036976-81
T-1248	January 12, 2007	Action Items for Thunder Meeting Minutes	ETH.MESH.00832555-56
T-1249		Material Specification for TVT Prolene Polypropylene Mesh Roll Stock (Revision 5)	ETH.MESH.02219202-10
IV. c. Catherine Beath Exhibits			
Exhibit #	**Date**	**Description**	**Bates #**
T-548	June 6, 2006	Executive Summary – Medical, Regulatory and Quality Systems Diagnostic, PowerPoint presentation	
T-1125		Ethicon GMB Chart	
T-1126		Ethicon WW Quality & Compliance Chart	
T-1127		Ethicon Quality and Regulatory Affairs Chart	
T-1128	August 2007	Ethicon QA/RA Organization Chart	

IV. c.	**Catherine Beath Exhibits (Continued)**		
T-1129		Franchise: Ethicon – Future Complaint Mgmt Global Organizational Structure and Flow Chart	
T-1130		Complaint Handling Flow (Typical) – Designated Complaint Handling Unit: Worldwide Customer Quality (WCQ) Chart	
T-1131	May 2009	Ethicon 2009 Strategic Plan, PowerPoint presentation	
T-1132		Our Credo	
T-1133	2009	RAPS Code of Ethics for Regulatory Professionals	
T-1134		FDA Introduction to Medical Device Labeling	
T-1135	March 8, 1991	FDA Device Labeling Guidance #G91-1 (blue book memo)	
T-1136	April 19, 2001	Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers	ETH.MESH.01203207-60
T-1137	March 1997	Medical Device Reporting for Manufacturers	
T-1138		Company Procedure for US Regulatory Affairs Review of Promotion and Advertising Material for Medical Devices (Revision 1)	ETH.MESH.08164248-56
T-1139	June 12, 2006	Promotion and Advertising of Medical Devices, PowerPoint presentation	ETH.MESH.08164257-no Bates
T-1140		CV of Catherine V. Beath	
T-1141	October 13, 2008	Emails Re: FDA Public Health Notice on Surgical Mesh for POP and SUI – URGENT	ETH.MESH.00329112-13
T-1142	October 17, 2008	Email Re: confidential: FDA Notification documents	ETH.MESH.00066957
T-1143	November 25, 2008	Email Re: FDA PHN of Surgical Mesh	ETH.MESH.00856006
T-1144		FDA Public Health Notification, with AdvaMed revisions	ETH.MESH.00856011-13
T-1145	October 20, 2008	FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence	

IV. c.	**Catherine Beath Exhibits (Continued)**		
T-1146	October 21-22, 2008	Emails Re: Information about FDA notification on use of mesh in pelvic surgery	ETH.MESH.00764399-400
T-1147	October 14, 2008	Voice mail message from Kevin Mahar to ETHICON Women's Health & Urology U.S. Sales & Marketing Organization	ETH.MESH.00066960
T-1148	October 21, 2008	FDA Notification About Use of Surgical Mesh to Treat Pelvic Organ Prolapse and Stress Urinary Incontinence – Standby for Media/Analyst Inquiries	ETH.MESH.00164023-25
T-1149	2008	The Choice to End Stress Urinary Incontinence patient brochure	ETH.MESH.03458123-38
T-1150	2009	Treatment Options for Stress Urinary Incontinence patient brochure	ETH.MESH.00161969-84
T-1151	2012	Stress Urinary Incontinence patient brochure	ETH.MESH.05815791-802
T-1152	January 28, 1998	510k Summary – K974098 (Tension Free Vaginal Tape (TVT) System)	
T-1153	September 22-24, 2003	Emails Re: additional questions on the GYNECARE TVT insert	ETH.MESH.00198483-86
T-1154	November 26, 2003	Email Re: Professor de Leval's comments and thoughts consecutive to recent email and phone call exchanges	ETH.MESH.00865625-27
T-1155	[Redacted]	[Redacted]	ETH.MESH.00333217-48
T-1156	October 25, 2007	Emails Re: TVT O versus TVT Secur efficacy and safety rates	ETH.MESH.00647410-16
T-1156A	October 25, 2007	Emails Re: TVT O versus TVT Secur efficacy and safety rates	ETH.MESH.00647410-16
T-1157	November 2, 2007	Emails Re: Meeting [Redacted] to discuss TVT Secur performance	ETH.MESH.00330334-37
T-1158	November 2-3, 2007	Emails Re: URGENT: Meeting with the Australian Regulator to discuss TVT Secur performance	ETH.MESH.02154877-81
T-1159	November 30-December 2, 2007	Emails Re: TVT-S Australia standby	ETH.MESH.00128978-80
T-1160	November 5, 2007	Emails Re: TVT complaint telecom 5 November	ETH.MESH.00827168-69
T-1161		TVT-Secur Quality Board, PowerPoint presentation	

IV. c.	**Catherine Beath Exhibits (Continued)**		
T-1162	June 2-6, 2009	Emails Re: TVT-S follow up	ETH.MESH.06070148-54
T-1163	February 2004	2004 Strategic Alignment – Regulatory Affairs & Quality Assurance, PowerPoint presentation	
T-1164	August 2005	Ethicon Quality & Compliance, PowerPoint presentation	
T-1165		2005 Strategic Planning Process, PowerPoint slides	
T-1166	2005	2005 Performance and Development Plan Summary for Catherine Beath	ETH.MESH.08470696-703
T-1167	2005	2005 Performance and Development Plan Summary for Cindy Crosby	ETH.MESH.08470976-87
T-1168	March 10, 2008	Letter from Department of Health and Human Services, with Establishment Inspection Report	ETH.MESH.07220424-40
T-1169	May 15-20, 2009	Emails RE: ERCC Meeting May 18	ETH.MESH.02249524-26
T-1170	May 18, 2009	Ethicon Regulatory Compliance Council Meeting Action Items	
T-1171	November 13-16, 2009	Emails RE: Secur Archiv [sic]	ETH.MESH.02254042
T-1172		PR-0000018 rev. 15 Appendix II: Ethicon Franchise Records Retention Schedule	
T-1173		Trigger Acronyms, Trigger Event Titles & Trigger Event Descriptions	
T-1174		Gynecare Gynemesh PS for Pelvic Organ Prolapse, website information	
T-1175	November 2, 2007	Emails RE: URGENT: Meeting with the Australian Regulator to discuss TVT Secur performance	ETH.MESH.06051016-20
T-1176	April 30-May 9, 2002	Emails Re: Ethicon Inc. Audit Report, with Audit Report attached	ETH.MESH.02249638-42
T-1177	May 26, 2009	All Active CAPA's chart	ETH.MESH.02250914-45
T-1178	February 28-29, 2012	Independent MD&D Sector Audit – Confidential Report	ETH.MESH.07724068-80
T-1179	March 30, 2011	Emails Re: Pelvic Floor Mesh	ETH.MESH.02252640-42
T-1180	July 13-14, 2011	Emails Re: FDA Health Notification	ETH.MESH.02253078-79
T-1181	September 7-16, 2004	Emails Re: Ongoing TVT-O Action Items	ETH.MESH.06884728-32

IV. c.	**Catherine Beath Exhibits (Continued)**		
T-1182	2009	Gynecare TVT Instructions for Use	ETH.MESH.03427878-946
T-1183	September 8-9, 2011	Surgical Mesh for Treatment of Women With Pelvic Organ Prolapse and Stress Urinary Incontinence – FDA Executive Summary	ETH.MESH.02253333-415
T-1184	January 3, 2012	Letter from FDA to Catherine Beath Re: Postmarket Surveillance (PS) Study: PS120046 (Trade Name: Gynemesh Prolene Soft (Polypropylene) Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair) – K013718	ADVAMED00014388-91
T-1185	January 3, 2012	Email Re: 522 Guidance Document	ETH.MESH.05603819-20
T-1186	April 2012	Letter from FDa to Brian Kanerviko Re: PS120043 (Reference PMA/510(k): K071512)	ETH.MESH.04474308-12
T-1187	May 1, 2012	Regulatory Contact Report	ETH.MESH.04474786
T-1188	May 3-15, 2012	Emails Re: International Impact US 522 Orders and Decision, with Assessment from Irene Leslie and Pat Napoda attached	ETH.MESH.08366243-45
T-1189	May 14-15, 2012	Emails Re: CONFIDENTIAL: Advanced Notice of U.S. Gynecare Commercialization Decision Announcement	ETH.MESH.04925364-66
T-1190	May 17, 2012	Emails Re: 522 Gynecare Pelvic Floor	ETH.MESH.04925345-47
T-1191	May 18-20, 2012	Emails RE: RA comments on EG WW Commercialization Regional Plan	ETH.MESH.04925322-23
IV. d.	**Chrisophe Vailhe Exhibits**		
Exhibit #	**Date**	**Description**	**Bates #**
T-1097		CV of Christophe N.P. Vailhe	
T-1098	January 28, 2010	Announcement of transfer of Christophe Vailhe to EWH&U R&D	ETH.MESH.07194129
T-1099	October 14, 2011	Polypropylene Mesh for Pelvic Floor Repair (PFR) – Focus on Mesh Exposure – Road to Improvement	ETH.MESH.03719177-95
T-1100	May 10, 2004	Emails Re: Mesh for TVM	ETH.MESH.00584846-47
T-1101	November 13-15, 2006	Emails Re: Pelvic Floor/Mesh Strategy	ETH.MESH.03160750-52
T-1102	June 2, 2006	Ethicon Expert Meeting – Meshes for Pelvic Floor Repair	ETH.MESH.00870466-76

IV. d.	**Chrisophe Vailhe Exhibits (Continued)**		
T-1103	January 29, 2012	Email Re: WH&U Position Paper: Erosion, with Polypropylene Mesh for Pelvic Floor Repair (PFR) report attached	ETH.MESH.04038031-55
T-1104	February 23, 2011	Emails Re: My MosaIQ – Ethicon Subscription Alerts – Maher paper	ETH.MESH.03031629-31
T-1105	October 21, 2010	Email Re: Mesh Erosion	ETH.MESH.00584561
T-1106	April 8, 2008	Email Re: Interim Report Mesh Implants Pelvic floor Prof. Klosterhalfen	ETH.MESH.02227221-22
T-1107	September 9, 2009	Email Re: EN_1251273177_Netz-Explantate_mpu_21777_ue_ed.doc, with translation of interim expert report on histology of 172 human pelvic floor mesh explants attached	ETH.MESH.02157878-80
T-1108	January 9, 2012	Email Re: Mesh Exposure – Ethicon Position – Short List	ETH.MESH.08579092-93
T-1109	February 1, 2012	Email Re: Exposure Position Norderstedt 2012.pptx	ETH.MESH.07200381
T-1110	February 2, 2012	Mesh Exposure – Ethicon Position, PowerPoint presentation	ETH.MESH.07200382-no Bates numbers
T-1111	March 5, 2012	CDMA Meeting Minutes – 2012	ETH.MESH.04548236-42
T-1112	November 1, 2010	Letter Re: Investigation into mesh erosion in pelvic floor repair	ETH.MESH.07192033-41
T-1113	February 17, 2011	Email Re: Sales reps in UK	ETH.MESH.07192242
T-1114	May 18, 2011	Investigating Mesh Erosion in Pelvic Floor Repair, PowerPoint presentation	ETH.MESH.02589032-79-no Bates numbers
T-1115	May 18-July 21, 2011	Emails Re: Mesh erosion report attached	ETH.MESH.07198825-28
T-1116	June 22, 2011	Investigating Mesh Erosion in Pelvic Floor Repair, PowerPoint presentation	ETH.MESH.07192929-no Bates numbers
T-1117	January 20, 2011	PA Consulting Group – Mesh Erosion Interview-Surgeon (Minutes of Meeting)	ETH.MESH.07192012-14
T-1118	January 18, 2011	PA Consulting Group – Mesh Erosion Interview-Pathology (Minutes of Meeting)	ETH.MESH.07192412-14
T-1119	January 14, 2005	Clinical Expert Report of Charlotte D. Owens	ETH-07152–58

IV. d.	**Chrisophe Vailhe Exhibits (Continued)**		
T-1120	February 9, 2011	Email Re: You have been selected – Forces on the pelvic floor – challenge to determine	ETH.MESH.07197998
T-1121	April 11-May 18, 2011	Emails Re: Forces in the pelvic floor, with Cobb article attached	ETH.MESH.07192872-77
T-1122	February 16, 2011	Biomechanical consideration for Pelvic floor mesh design	ETH.MESH.02185584-605
T-1123	January 16, 2012	Email Re: Biomechanics of the pelvic floor, with Ethicon Position Paper attached	ETH.MESH.07200224-44
T-1124	May 12, 2011	Altman D, et al. "Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse." N Engl J Med 2011;364(19):1826-36	
IV. e.	**Daniel Burkley Exhibits**		
Exhibit #	**Date**	**Description**	**Bates #**
T-268		CV of Daniel Fredrick Burkley	
T-269	April 1-3, 2009	Emails Re: Analytical characterization – Optimization of Structure	ETH.MESH.02184435-36
T-270		Our Credo	
T-271		Our Ethical Code for the Conduct of Research and Development	
T-272	January 26-March 1, 2012	Emails Re: Polypropylene mesh	ETH.MESH.07226377-79
T-273	February 28-29, 2012	Emails Re: Your Professional Opinion	ETH.MESH.04038180-81
T-274	January 26-March 5, 2012	Emails Re: Polypropylene mesh	ETH.MESH.04937874-76
T-275	March 6, 2012	Response to email from Clare Huntington 26 January 2012 (15:38) with attached publication: Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants, Int Urogynecol J 2010;21:261-270	ETH.MESH.07212397-98

IV. e.	**Daniel Burkley Exhibits (Continued)**		
T-276	March 12, 2012	Letter Re: Response to email from Clare Huntington 26 January 2012 regarding publication by Clave et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants, Int. Urogynecol J 2010;21:261-270	ETH.MESH.07205369-70
T-277	2009	Clave A et al. "Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants." Int Urogynecol J 2010;21:261-270	
T-278	March 7, 2012	Emails Re: Information on PROLENE Suture and PROLENE Mesh	ETH.MESH.07226404-05
T-279	April 2008	Interim report mesh explants pelvic floor repair	ETH.MESH.000006636
T-280	June 2009	Intermediate Report – Prolapse Mesh Explants	ETH.MESH.02157879-80
T-281		Research findings, with handwritten notes	ETH.MESH.07726805-17
T-282	October 15, 1992	Seven Year Data for Ten Year Prolene Study: ERF 85-219	ETH.MESH.05453719-27
T-283	December 14, 2010	ERM team meeting Minutes	ETH.MESH.02588977-78
T-284		Revenue from different firms	ETH.MESH.03699547-no Bates numbers
T-285	May 18, 2011	Investigating Mesh Erosion in Pelvic Floor Repair, PowerPoint presentation	ETH.MESH.02589032-79
T-286	March 24-31, 2011	Emails R: Thanks & pictures	ETH.MESH.07198250
T-287	2007	Costello CR, et al. "Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants From a Single Patient." Surg Innov. 2007;14:168-76	
T-288		Hernia Mesh Development, Incontinence (TVT) Development, and Pelvic Floor Development Timeline	ETH.MESH.01816988-no Bates numbers
T-289		Porosity Measurements of Various Meshes chart	ETH.MESH.02183537-no Bates numbers
T-290		Porosity Measurements of Prolene Meshes chart	ETH.MESH.05443495-no Bates numbers

IV. e.	**Daniel Burkley Exhibits (Continued)**		
T-291		Operating Procedure for Optical Evaluation to Determine Porosity of Mesh Samples Using the Nikon Stereomicroscope and Image-Pro Plus Image Analysis System	ETH.MESH.05443059-64
T-292		Pore Size Measurement of Surgical Mesh Products	ETH.MESH.05443077-85
T-293	January 18-20, 2006	Emails Re: TVT – TVT-O Specifications	ETH.MESH.00585906-09
T-294	November 14, 2007	Mesh Testing, PowerPoint presentation	ETH.MESH.02212596-no Bates numbers
T-295	March 2005	Cobb WS, et al. "The Argument for Lightweight Polypropylene Mesh in Hernia Repair." Surgical Innovation 2005;12(1):T1-T7	ETH.MESH.01424029-35
T-296	2005	Klosterhalfen B, et al. "The lightweight and large porous mesh concept for hernia repair." Expert Rev Med Devices 2005;2(1)	
T-297		Product Quality Plan for Gynecare Gynemesh XL	
T-298	April 25, 2002	Corporate Product Characterization – Product Performance Evaluation Group (Test Report)	ETH.MESH.01808729-41
T-299		Solving the Device Design Puzzle	ETH.MESH.05918082-116
T-300	March 19, 2003	Corporate Product Characterization – Product Performance Evaluation Group (Final Test Report)	ETH.MESH.01218446-49
T-301	April 7, 2004	Interoffice Memorandum Re: Risk Assessment for Laser Cutting of D'art Gynemesh PS Implants	ETH.MESH.07190442-46
T-302	November 10, 2000	New York Times article, "Company News; Sunoco Agrees to Buy Mitsubishi's Aristech Chemical."	
T-303	August 25-26, 2011	Emails Re: Braskem…A Little History	ETH.MESH.06261965-67
T-304	January 31-February 3, 2003	Emails Re: Athos: Analytical Testing	ETH.MESH.02268613-14

IV. e. Daniel Burkley Exhibits (Continued)			
T-305	February 11-21, 2003	Emails Re: ATHOS: PROLENE Additives and Exposure, with J. Karl's memo indicating the R&D specifications for various additives used in Prolene resin attached	ETH.MESH.02268618-21
T-306	April 27, 2005	Emails Re: PROLENE vs polypropylene	ETH.MESH.03908707-08
T-307	November 2003	Material Safety Data Sheet (Product Name: C4001 Polypropylene Homopolymer)	
T-308	March 9, 2006	Interim Report for TVT-Secur Implant (Test and Control Article Material Characterization Program)	ETH.MESH.00750766-69
T-309	April 26-27, 2010	Emails Re: surface area	ETH.MESH.02185004
T-310	April 19, 2012	Material Safety Data Sheet (Ethylene Oxide)	
IV. f. Daniel Smith Exhibits			
Exhibit #	**Date**	**Description**	**Bates #**
T-215		Design 30(b)(6) Topic 1 (TVT Project Names)	DEPO.ETH.MESH.00000067
T-216		Amended Notice to Take Oral Deposition of Defendant Through Designated Witness Regarding TVT-O	
T-217		Gynecare TVT-Obturator DH1019 (Book 1 of 7)	ETH.MESH.00259047-513
T-218	May 8-10, 2013	Emails Re: Production of Policy before design 30(b)(6) deposition	
T-219		Operating Procedure for Design Failure Modes and Effects Analysis (dFMEA), with edits	
T-220	May 8, 2013	Operating Procedure for Design Failure Modes and Effects Analysis	
T-221	June 20, 2003	Emails Re: Design Control	ETH.MESH.01814371-72
T-222		Work Instruction for New Product Design Control (PR 800-011), Version 5, Appendix I-V, with edits	ETH.MESH.01814384-400
T-223		Gynecare TVT-Obturator DH1019 (Book 2 of 7)	ETH.MESH.03361541-2130)
T-224		Gynecare TVT-Obturator DH1019 (Book 3 of 7)	ETH.MESH.01804278-592

IV. f.	**Daniel Smith Exhibits (Continued)**		
T-225		Gynecare TVT-Obturator DH1019 (Book 4 of 7)	ETH.MESH.03362131-630
T-226		Gynecare TVT-Obturator DH1019 (Book 5 of 7)	ETH.MESH.00259514-60002
T-227		Gynecare TVT-Obturator DH1019 (Book 6 of 7)	ETH.MESH.00859014-681
T-228	2003	Target Sheet (Design History: DH1019 (bk6) – DH1021 (bk1))	ETH.MESH.01319500-20123
T-229	March 5-16, 2004	Emails Re: TVTO training Carmel Ramage	ETH.MESH.03364540-44
T-230	August 18, 2004	Email Re: Dr. Jensen Follow Up	ETH.MESH.06884516-17
T-231	June 2, 2003	Email Re: My notes from the Thursday evening presentation 5/22/03 and Friday's surgery	ETH.MESH.00862727-28
T-232	June 22, 2004	Email Re: GYNECARE TVT Obturator Global Launch Update – Issue 4	ETH.MESH.06881589-91
T-233	August 5-17, 2004	Emails Re: TVTO Dr. Feagins case follow up	ETH.MESH.01815505-13
T-234	September 7-8, 2004	Emails Re: Ongoing TVT-O Action Items	ETH.MESH.06884726-27
T-235	September 7-14, 2004	Emails Re: Ongoing TVT-O Action Items	ETH.MESH.00864493-96
T-237	August 5-17, 2004	Emails Re: TVTO	ETH.MESH.06881576-80
T-238	May 4-5, 2004	Emails Re: TVT-O	ETH.MESH.00864407-08
T-239	February 19, 2004	Email Re: TVT-O recognition Submission JANICE FOR YOUR COMMENTS!!!!!!!	ETH.MESH.06892171-72
T-240	September 7-8, 2004	Emails Re: Ongoing TVT-O Action Items	ETH.MESH.00864490-92
T-241		Gynecare TVT Obturator System Tension-free Support for Incontinence, PowerPoint presentation	ETH.MESH.06856958-no Bates numbers
T-242	January 28-29, 2009	Emails Re: TVT-O resin Minute Jan 31th	ETH.MESH.06858146-47
T-243		Test Method for the Thickness of Mesh (Revision History for TM403-145)	ETH.MESH.06858314-18
T-244		Work Instructions for Device Design Risk Management	ETH.MESH.08438961-65

IV. f.	**Daniel Smith Exhibits (Continued)**		
T-245	February 14, 2003	Due Diligence Growth Opportunity Online	ETH.MESH.06873447-58
T-246	March 4, 2003	Gynecare R&D Monthly Update – March	ETH.MESH.00858094-95
T-247	June	Gynecare R&D Monthly Update – June	ETH.MESH.00858092-93
T-248	June 24, 2003	Email Re: Project Mulberry	ETH.MESH.02180737
T-249	January 16, 2007	History of TVT-O	ETH.MESH.03932909-11
T-250		Top Ten Reason to Pursue…Gynecare TVT Obturator System, PowerPoint presentation	ETH.MESH.00857891-93
T-251		Brand equity chart for TVT "R," TVT "O," TVT Secur "H," and TVT Secur "U"	ETH.MESH.00858891
T-252	January 22-23, 2004	Gynecare Sales Training Launch Meeting, PowerPoint presentation	ETH.MESH.00857821-922
T-253	July 15-August 8, 2003	Emails Re: I: Transient Leg Pain with MULBERRY	ETH.MESH.03803462-65
T-254		TVT Obturator DDSA – Version 2 (PR602-003)	ETH.MESH.00259473-503
T-255	March 29, 2004	Letter from Professor Jean de Leval at University of Liege	ETH.MESH.02180759-61
T-256	July 23-24, 2003	Emails Re: TOVT development	ETH.MESH.00864101-02
T-257	August 7-8, 2007	Emails Re: Adventures with TVT Secur	ETH.MESH.06861426-29
T-258	August 12-15, 2003	Emails Re: Aug 11 program	ETH.MESH.00864131-33
T-259		The following are the high level f/u's from today's meeting	ETH.MESH.03926030-31
T-260		Gynecare R&D Monthly Update – May	ETH.MESH.00858096-97
T-261	May 29, 2003	Descriptions, Clinical Plans, and Action Items for Ethicon Studies	ETH.MESH.00260020-21
T-262	June 12-17, 2003	Emails Re: Discussion 11th June 2003	ETH.MESH.01815611-13
T-263	June 6, 2003	Mulberry Weekly Meeting Minutes for 6/3/03	ETH.MESH.00858175-77

IV. f.	**Daniel Smith Exhibits (Continued)**		
T-264	December 24, 2003-January 16, 2004	Emails Re: Dedication	ETH.MESH.06164409-10
T-265	Spring 2010	R&D Co-Op Welcome Guide	ETH.MESH.06260647-71
T-266	May 14, 2001	Target Sheet (Design History: DH0263-DH0278)	ETH.MESH.01316727-65
T-267	May 14, 2001	Target Sheet (Design History: DH0263-DH-0278)	ETH.MESH.01317508-613
T-406		The history of TVT	ETH.MESH.03932912-14
T-407	1996	Ulmsten U, et al. "An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence." Int Urogynecol J 1996;7:81-86	ETH.MESH.05795664-69
T-408		TVT: Insights into the Making of a Revolution, PowerPoint presentation	ETH.MESH.06859904-no Bates numbers
T-409	November 1999	Asset Purchase Agreement between Johnson & Johnson and Medscand	ETH.MESH.05972834-66
T-410	August 18-November 7, 2005	Emails Re: TVT Records	ETH.MESH.05220458-64
T-411	2000	International Standard (ISO) 14971 – Medical Devices – Application of risk management to medical devices	
T-412		Company Procedure for the Ethicon Product Development Process (PDP)	ETH.MESH.06477464-81
T-413		Operating Procedure for Failure Modes and Effects Analysis Application (aFMEA) or Design (dFMEA)	ETH.MESH.03742864-91
T-414		Company Procedure for Medical Device Risk Management Plan (Revision 7)	ETH.MESH.03742571-97
T-415	January 28, 1998	510k Notification for Tension Free Vaginal Tape (TVT) System – K974098	
T-416		Risk Management Report (Legacy) for TVT and TVT-O	ETH.MESH.01265223-39
T-417		Risk Management Report (Legacy) for TVT and TVT-O (Revision 2)	ETH.MESH.01268264-77
T-418		Form for Internal Audit Corrective Action Plan (Revision 4)	ETH.MESH.03652924-55

IV. f.	**Daniel Smith Exhibits (Continued)**		
T-419	February 24, 2006	Memo Re: TVT Laser Cut Mesh (LCM) Risk Analysis Summary	ETH.MESH.00302105-06
T-420		Risk Management Report for TVT Laser Cut Mesh (LCM) (Revision 2)	ETH.MESH.01310061-65
T-421		Risk Management Report for TVT Laser Cut Mesh (LCM) (Revision 3)	ETH.MESH.01310476-81
T-422	November 9, 2010	TVT Classic IFU Revision Project: Design Requirements Waiver Rationale Memo	ETH.MESH.00748213-78
T-423		Physicians Participating in Validation/Cadaver Labs for TVT Products	
T-424		Pelvic Mesh Litigation: DHF and eDHF Collection and Production	DEPO.ETH.MESH.00000068-73
T-425		Amended Notice to Take Oral Deposition of Defendant Through Designated Witness Regarding TVT-S	
T-426		Memo Re: TVT Secur Lessons Learned Review	ETH.MESH.00858636-41
T-427	July 18, 2005	Corporate Product Characterization Plan for Gynecare TVT S (Secur)	ETH.MESH.04939148-57
T-428		Gynecare TVT Secur, PowerPoint presentation	ETH.MESH.01150009-no Bates numbers
T-429	2007	Gynecare TVT Secur Competitive Product Update, PowerPoint presentation	ETH.MESH.06861473-no Bates numbers
T-430		Daniel Smith highlights at J&J	ETH.MESH.06860553-58
T-431		Company Procedure for the Ethicon Product Development Process (PDP)-Design Controls, Revision History for PR800-011	ETH.MESH.04316544-62
T-432		Company Procedure for Design Changes to Existing Products-Revision History for PR800-012-Draft (Revision 11)	ETH.MESH.00363605-25
T-433		Operating Procedure for Failure Modes and Effects Analysis Application (aFMEA) or Design (dFMEA), Draft Re-write (40709)	ETH.MESH.05432198-224
T-434		Eth mesh 00752894 TOC dhf0000120.xls	
T-435		Pictures of Mesh Implant	
T-436	October 7, 2004	Email Re: TVTx – Next Generation TVT "Project INITIATION"	ETH.MESH.05456924-25

IV. f.	**Daniel Smith Exhibits (Continued)**		
T-437	November 22, 2004	2004 Strategy Tree Project Definition (Next Generation TVT-x)	ETH.MESH.00259042
T-438	November 30, 2004	Development Contract for TVT-Next (TVTx)	ETH.MESH.01217673-90
T-439	April 20-25, 2005	Emails Re: TVT SECUR Minutes-Team Meeting April 12th 2005_Agenda April 19th 2005	ETH.MESH.06274935-38
T-440	2005	Product Specification for Gynecare TVT Secur (Revision B)	ETH.MESH.01410044-47
T-441		Gynecare Finger Pad Detail Drawings	ETH.MESH.05554367-71
T-442	2005	Process Specification for Gynecare TVT Secur (Revision B)	ETH.MESH.04385192-97
T-443	February 27, 2006	Design Requirements Matrix: Relationship between User Needs, Intended Use, Design Requirements, Design Outputs, Design Verification, and Design Validation (Version 4)	ETH.MESH.05502894-928
T-444	February 27, 2006	Design Validation Report-(Product) Report # TVTSDVLPRD2 – Gynecare TVT Secur System	ETH.MESH.01592178-88
T-445	2005	Traditional 510k Notification for Gynecare TVT Secur System – K052401	ETH.MESH.07876572-819
T-446		Gynecare TVT Secur System Design Validation Report (Product) Report # TVTSDVLPRD1	ETH.MESH.02135955-68
T-447	October 25-29, 2007	Emails Re: TVT O versus TVT Secur efficacy and safety rates	ETH.MESH.00642325-31
T-448	August 18, 2004	Human Cadaver Wetlab Report/Results DRAFT	ETH.MESH.06869750-53
T-449	February 8, 2005	Final Report: Ethicon Study No. SO04/2-2-1 – A 3 month pre-clinical trial to assess the fixation force of a new TVT (TVTx) in the sheep model	ETH.MESH.01037530-45
T-450	2006	Rezapour M, et al. "A 3-month preclinical trial to assess the performance of a new TVT-like mesh (TVTx) in a sheep model." Int Urogynecol J 2006.	ETH.MESH.00034720-24
T-451	October 26-27, 2004	Emails Re: Results of TVTx preclinical trial	ETH.MESH.05537701
T-452	August 23, 2005	Final Report, PSE Accession Number 05-0395, Project Number 67379 (EDHF0000120)	ETH.MESH.00749504-17

IV. f.	**Daniel Smith Exhibits (Continued)**		
T-453	August 23, 2005	Final Report, PSE Accession Number 05-0396, Project Number 67379 (EDHF0000120)	ETH.MESH.00749518-41
T-454	December 2, 2005	Clinical Expert Report of Martin Weisberg, M.D.	ETH.MESH.03714002-18
T-455	August 23, 2005	Clinical Expert Report of Martin Weisberg, M.D.	ETH.MESH.03714599-614
T-456	August 30-September 15, 2005	Emails Re: clinical expert report	ETH.MESH.03905619-21
T-457	May 27, 2008	Risk Benefit Analysis for TVT Secur	ETH.MESH.00853802-06
T-458		A Pilot Study of the Gynecare TVT Secur System (Tension-free Support for Incontinence) for the Treatment of Stress Urinary Incontinence (Protocol 300-05-002)	ETH.MESH.00538202-42
T-459	November 21, 2005	Gynecare TVT Secur Process Qualification Completion Report (Manufacture and subsequent operations of the Inserter Body) : Protocol # 05/157; Version 1	ETH.MESH.00752863-93
T-460	November 22, 2005	Process Qualification Completion Report: Inserter Assembly – Welded (Protocol # 05/149; Version 1)	ETH.MESH.03648795-810
T-461	June 6, 2006	Design Transfer Checklist – Project Name: Process at Ethicon SaRL and Ethicon GmbH for the TVT Secur System	ETH.MESH.01409412-22
T-462	May 18, 2006	Email Re: Design Transfer Checklist Discussion, 5/16/06	ETH.MESH.0554680
T-463		Revision History for TVT Secur application FMEA (Version 1)	ETH.MESH.05534022-no Bates numbers
T-464		Application FMEA for TVT Secur (Revision 2)	ETH.MESH.00823549-53
T-465		Design FMEA for TVT Secur (Version 1)	
T-466		Potential Failure Mode and Effects Anlysis, Process FMEA-100152 (Revision A)	ETH.MESH.01407837-no Bates numbers
T-467		Risk Management Report – TVT Secur System (Revision A (Development))	ETH.MESH.00752921-25

IV. f. Daniel Smith Exhibits (Continued)			
T-468		Risk Management Report – TVT Secur System (Revision B (Development))	ETH.MESH.00752928-32
T-469		TVT Secur Harms/Hazards Table (Version A)	ETH.MESH.00752933-34
T-470		Risk Management Report – TVT Secur System (Revision 1)	ETH.MESH.05534009-13
IV. g. David Robinson Exhibits			
Exhibit #	**Date**	**Description**	**Bates #**
T-922		Incontinence Preceptors (Alpha) chart	ETH.MESH.00679574-92
T-923	December 2-3, 2003	Emails Re: Is there a good time when we can speak tomorrow if possible or sometime this week?	ETH.MESH.02270949-51
T-924	October 25-29, 2007	Emails Re: TVT O versus TVT Secur efficacy and safety rates	ETH.MESH.00642325-31
T-925	August 2, 2010	Clinical Evaluation Report – Gynecare TVT Tension-free Vaginal Tape/Tension-free Vaginal Tape Accessory Abdominal Guide	ETH.MESH.01795834-73
T-926	August 19	Incontinence Platform-WW Marketing Team Update, PowerPoint presentation	ETH.MESH.02105223-no Bates numbers
T-927		Gynecare TVT Secur – Tension-free Support for Incontinence, PowerPoint presentation	ETH.MESH.02248848-no Bates numbers
T-928	June 20, 2006	Emails Re: Clinical strategy for SECUR	ETH.MESH.01782850-52
T-929	February 27, 2009	Email Re: TVT WORLD Board meeting presentation, with TVT WORLD PowerPoint presentation attached	ETH.MESH.00134794-95, no Bates numbers
T-930	June 9, 2006	Emails Re: meeting	ETH.MESH.03171093-94
T-931	September 12, 2006	Confidential Interim Statistical Report: An Evaluation of the GYNECARE TVT SECUR System for the Treatment of Stress Urinary Incontinence	ETH.MESH.04499687-742
T-932	November 14, 2006	Emails Re: TVT-S Preceptor Meeting Discussion	ETH.MESH.00153967-68
T-933	September 20, 2006	Email Re: TVTS Complaint up to 20 September 06.ppt, with PowerPoint attached	ETH.MESH.00839918-19, no Bates numbers

IV. g.	**David Robinson Exhibits (Continued)**		
T-934	March 14, 2007	Email Re: Conf call tomorrow, with "A Multicenter, Open-Label, Randomized, Non-Comparative Study Designed to Obtain Clinical Information on the GYNECARE TVT SECUR System Tension-free Support for Incontinence" PowerPoint presentation attached	ETH.MESH.03922618-19, no Bates numbers
T-935	June 2012	Clinical Study Report: Evaluation of the TVT Secur System for Stress Urinary Incontinence	ETH.MESH.06479808-85
T-936		Karram M, et al. "An Evaluation of the Gynecare TVT Secur System (Tension-Free Support for Incontinence) for the Treatment of Stress Urinary Incontinence." Int Urogynecol J 2007;18(Suppl. 1):S3 (Abstract only)	ETH.MESH.00147163
T-937	June 1, 2007	CDMA Europe Meeting – Urinary Incontinence Platform (Meeting Minutes)	ETH.MESH.03913651-55
T-938	July 2009	Clinical Study Report: An Evaluation of the GYNECARE TVT SECUR System (Tension-free Support for Incontinence) For The Treatment of Stress Urinary Incontinence	ETH.MESH.02916532-615
T-939	December 15-20, 2006	Emails Re: TVT-S Cookbooks	ETH.MESH.01784428-35
T-940	2005	Gynecare TVT Secur System Instructions for Use (IFU)	ETH.MESH.02340568-90
T-941	March 7, 2007	Emails Re: DRAFT of the latest "cookbook" after my trip to Germany	ETH.MESH.00311811-13
T-942	May 4, 2007	Gynecare TVT Secur System: Key Technical Points	ETH.MESH.00163952-60
T-943		Summary of Gynecare TVT Secur System Critical Steps	ETH.MESH.00523617-18
T-944	February 5, 2007	Email Re: Summit Meeting – TVT Breakout Session – Moderator Script	ETH.MESH.00729815-21
T-945	December 15-17, 2006	Emails Re: TVT SECUR Conf Call Summary	ETH.MESH.00153882-85
T-946	November 8-12, 2007	Emails Re: Australia update and telephone call with Prof Frazer	ETH.MESH.00327060-63
T-947	April 14, 2008	Issue Report (Tracking # 10100069733)	ETH.MESH.02634983-93

IV. g.	**David Robinson Exhibits (Continued)**		
T-948	January 8-9, 2008	Emails Re: TGA Meeting	ETH.MESH.05208708-10
T-949	2011	Hinoul P, et al. "A Randomized, Controlled Trial Comparing an Innovative Single Incision Sling With an Established Transobturator Sling to Treat Female Stress Urinary Incontinence." The Journal of Urology 2011;185:1-7	ETH.MESH.00576529-40
T-950	January/ February 2012	Hota LS, et al. "TVT-Secur (Hammock) Versus TVT-Obturator: A Randomized Trial of Suburethral Sling Operative Procedures." Female Pelvic Med Reconstr Surg 2012;18:39-43	ETH.MESH.04474756-60
T-951	March 24, 2008	Issue Report (Tracking # 10100068346)	ETH.MESH.02634889-99
T-952	September 30, 2008	Issue Report (Tracking # 10100079562)	ETH.MESH.02635648-58
T-953	March 19, 2010	Email Re: Information regarding Scion	ETH.MESH.06927248-49
T-955	January 2010	Ethicon Women's Health and Urology Brand Equity Study-Final Report, PowerPoint presentation	ETH.MESH.03643186-no Bates numbers
T-956	May 2003	Arrowhead Campaign notes	ETH.MESH.00756100-02
T-957	May 11, 2004	Emails Re: Revenue acceleration approaches	ETH.MESH.00128358-60
T-958	December 17, 2004-January 5, 2005	Emails Re: Important Laser cut mesh update	ETH.MESH.00440005-07
T-959	May 6, 2005	Email Re: Laser-cut Mesh	ETH.MESH.00526473
T-960	December 14, 2004	Comparison of Laser-Cut and Machine-Cut TVT Mesh to Meshes from Competitive Devices (BE-2004-1641)	ETH.MESH.01809080-81
T-961		Scope Discussion and General Development Considerations (Project Scion)	ETH.MESH.04048515-20
T-962	October 18, 2006	Emails Re: TVT SECUR	ETH.MESH.01822361-63
T-963	August 16, 2005	Email Re: TVT Laser Cut Mesh	ETH.MESH.00525573

IV. g.	**David Robinson Exhibits (Continued)**		
T-964	August 3-23, 2005	Emails Re: TVT Laser Cut Value Proposition and Forecast	ETH.MESH.04985249-52
T-965		The Gynecare TVT Family of Products, promotional material	ETH.MESH.00658453-58
T-966	2008	Gynecare TVT-Secur-Overview of 2008 Product (Complaints Reported as MDR Serious Injuries)	ETH.MESH.04081468-73
T-967		The Science of "What's Left Behind"…Evidence & Follow-Up of Mesh Use for SUI, PowerPoint presentation	ETH.MESH.00271641-no Bates numbers
T-968	March 7, 2006	Clinical Expert report by Martin Weisberg, MD, and David Robinson, MD	ETH.MESH.01784823-28
T-969	May 23-December 19, 2005	Emails Re: Lazer [sic] cut mesh	ETH.MESH.00687819-22
T-970	February 6, 2009	Email Re: CR Approved 2009-98, with Ethicon, Inc. Worldwide Complaint Reporting Statement PowerPoint slide attached	ETH.MESH.00007091-92
T-971	January 19-20, 2006	Emails Re: TVT-O Patient-Related Complaint Categories	ETH.MESH.01782154-56
T-972	January 26-27, 2005	Emails Re: TVT procedures	ETH.MESH.00067902-04
T-973	March 24-25, 2005	Emails Re: Hematoma	ETH.MESH.02271018
T-974	December 9-10, 2004	Emails Re: VOC on Laser cut mesh	ETH.MESH.01811770-72
T-975	February 6, 2006	Emails Re: TVT complications	ETH.MESH.00847536
T-976	April 28-May 7, 2008	Emails Re: Alert date: TVT SECUR complications paper, our file #10100071175	ETH.MESH.03531443-48
T-977	December 21, 2005	Emails Re: 10100015704 question	ETH.MESH.00845911-12
T-978	January 26-May 26, 2009	Emails Re: TVT Complications Statement 2008, with statement attached	ETH.MESH.02122903-07, no Bates numbers
T-979		Risk/Benefit Analysis Re: page 4, line 3 of Clinical Expert Report; Gynecare TVT Secur System	ETH.MESH.00823660
T-980	June 2, 2005	Issue Report (Tracking # 20012722)	ETH.MESH.02652985-87

IV. g.	**David Robinson Exhibits (Continued)**		
T-981	February 25, 2005	Issue Report (Tracking # 30005181)	ETH.MESH.02627466-71
T-982	February 18, 2005	Issue Report (Tracking # 30005157)	ETH.MESH.02627418-21
T-983	February 5-26, 2007	Emails Re: modified version of TVT-O [TOT] Procedure	ETH.MESH.00832937-39
T-984		Objections & Handling Statements, with handwritten notes	ETH.MESH.00143133-35
T-985	October 28, 2005	Email Re: forgot	ETH.MESH.00756984
T-986		"The Choice to End Stress Urinary Incontinence" patient brochure	ETH.MESH.08003263-78
T-987	March 6, 2006	Letter Re: Elongation Characteristics of Laser Cut PROLENE Mesh for TVT	ETH.MESH.01222075-79
T-988	May 5, 2005	Performance Evaluation of TVT U PROLENE Mesh: Mechanical Cut versus Laser Cut Study (LIMS # BE-2005-1920) Version 3	ETH.MESH.0669367-79
T-989	2011	Tincello DG, et al. "The TVT Worldwide Observational Registry for Long-Term Data: Safety and Efficacy of Suburethral Sling Insertion Approaches for Stress Urinary Incontinence in Women." The Journal of Urology 2011;186:2310-2315	
T-1262		Handwritten Q&A: "TVT: The Benefit"	
T-1263		Handwritten Q&A: "Would 1% Deaths Related to TVT Be too Much Risk?"	
T-1264		Handwritten Q&A: "Would 1% of Permanent Pelvic Pain Be too Much Risk?"	
T-1265		Ethicon, Inc. Worldwide Complaint-Reporting Statement (Most Significant Reported Complications through December 31, 2007)	ETH.MESH.01128704
T-1266	January 14-16, 2006	Emails Re: GYNECARE TVT Latest Complication Data	ETH.MESH.00692884-85

IV. g.	**David Robinson Exhibits (Continued)**		
T-1267	2004	Ward KL, et al. "A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: Two-year follow-up." American Journal of Obstetrics and Gynaecology 2004;190:324-31	ETH.MESH.00160131-38
T-1268	2001	Nilsson CG, et al. "Long-term Results of the Tension-Free Vaginal Tape (TVT) Procedure for Surgical Treatment of Female Stress Urinary Incontinence." Int Urogynecol J 2001;Suppl. 2:S5-S8	ETH.MESH.00658807-10
T-1269	December 2004	Nilsson CG, et al. "Seven-Year Follow-up of the Tension-Free Vaginal Tape Procedure for Treatment of Urinary Incontinence." Obstet Gynecol 2004;104:1259-62	ETH.MESH.03930120-23
T-1270	2008	Nilsson CG, et al. "Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence." Int Urogynecol J 2008;19:1043-1047	ETH.MESH.00355003-07
T-1271	2013	Nilsson CG, et al. "Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence." Int Urogynecol J 2013	ETH.MESH.08299913-17
T-1272		"5 Years of Proven Performance" patient brochure	ETH.MESH.00339437-42
T-1273		"Only Gynecare TVT Has Long-term Results You Can See…and Believe" patient brochure	ETH.MESH.00658058-65
T-1274		"Make Data and Safety Your Choice" brochure	ETH.MESH.01186068-72
T-1275		"The Choice to End Stress Urinary Incontinence" patient brochure	ETH.MESH.08003215-30
T-1276	April 24, 2009	Emails Re: green journal	ETH.MESH.03259439-40

IV. g.	**David Robinson Exhibits (Continued)**		
T-1277	December 2011	Tincello DG, et al. "The TVT Worldwide Observational Registry for Long-Term Data: Safety and Efficacy of Suburethral Sling Insertion Approaches for Stress Urinary Incontinence in Women." The Journal of Urology 2011;186:2310-15	ETH.MESH.04523637-42
T-1278		Gynecare TVT Instructions for Use (IFU)	ETH.MESH.02340504-67
T-1279		Tension-free Vaginal Tape (Gynecare TVT) System—Instructions for Use	
T-1280	December 17, 2004-January 5, 2005	Emails Re: Important Laser cut mesh Update	ETH.MESH.00440005-07
T-1281	August 28, 2006	Email Re: Photographs of LCM vs MCM	ETH.MESH.08334244
T-1282		Second half photo presentation, PowerPoint slides	ETH.MESH.00584527-no Bates numbers
T-1283	2007	Moalli PA, et al. "Tensile properties of five commonly used mid-urethral slings relative to the TVT." Int Urogynecol J 2007	ETH.MESH.00294195-203
T-1284		Design FMEA TVT LCM Project	ETH.MESH.01218019-no Bates numbers
T-1285	November 22-26, 2002	Emails Re: Mini TVT – mesh adjustment	ETH.MESH.03910418-21
T-1286	April 17, 2007	Email Re: shrinkage, with Factors Related to Mesh Shrinkage PowerPoint presentation attached	ETH.MESH.02319408-09, no Bates numbers
T-1287	May 26, 2000	Letter Re: Review of Biocompatibility Data on the Tension Free Vaginal Tape (TVT) System for Compliance to FDA G-95/ISO 10993/EN 30993	ETH.MESH.06852118-29
T-1288		Characteristics of Synthetic Materials Used in Prolapse and Incontinence Surgery, PowerPoint presentation	ETH.MESH.00838428-no Bates numbers
IV. h.	**Gregory Jones Exhibits**		
Exhibit #	**Date**	**Description**	**Bates #**
T-115		"Our Credo" Johnson & Johnson	
T-3138		Curriculum Vitae of Gregory Jones	
T-3139		Curriculum Vitae of Gregory Jones	ETH. MESH. 08164608-09
T-3140	May 22, 2003	Email Re: Must Read! Gynecare Document Hold Notice	ETH.MESH.00875544-46
T-3141		The history of TVT	ETH.MESH.03932912-14

IV. h. Gregory Jones Exhibits (Continued)			
T-3142	January 28, 1998	Tension Free Vaginal Tape (TVT) System 510(k) Notification K974098	ETH.MESH.08476210-342
T-3143	June 7, 2002	Emails Re: Dr. Alex Wang, Taiwan – reports of "tape rejection" with TVT	ETH.MESH.00409674-75
T-3144		Complaint Index	ETH.MESH.01950408-456
T-3145	June 15, 2001	Memo Re: Gynecare TVT Tension-free Support for Incontinence Patient Brochure (Resubmission of Materials per FDA requirements)	ETH.MESH.00144268-69
T-3146	2000	Patient Brochure: Freedom from Stress Urinary Incontinence It's within your control.	ETH.MESH.00144270-78
T-3147		Email Re: statement proposed for insertion in the package insert for TV	ETH.MESH.08505229
T-3148	March 30, 1999	Email Re: TVT Insert	ETH.MESH.00203456
IV. i. Joerg Holste Exhibits			
Exhibit #	**Date**	**Description**	**Bates #**
T-1192		Meshes/Devices Chart	
T-1193		Hernia Mesh Development, Incontinence (TVT) Development, and Pelvic Floor Development Timelines	
T-1194		Hernia Mesh Development, Incontinence (TVT) Development, and Pelvic Floor Development Timelines	ETH.MESH.01816988-90, no Bates numbers
T-1195	January 28, 1998	Letter from FDA Re: K974098 (Tension Free Vaginal Tape (TVT) System)	
T-1196		Material Specification for TVT Prolene Polypropylene Mesh Roll Stock (Revision 5)	ETH.MESH.02219202-10
T-1197		TVT Prolene Polypropylene Mesh Roll Stock Appendix II	ETH.MESH.09479067-68
T-1198	February 15-16, 2011	Emails Re: WG: Prosima +M clin strat, with German article and English translation attached	ETH.MESH.03146492-516
T-1199	April 22, 2009	Emails Re: Question on Monocryl absorption, with Cobb article attached	ETH.MESH.02148431-60
T-1200	2005	Cobb WS, et al. "The Argument for Lightweight Polypropylene Mesh in Hernia Repair." Surgical Innovation 2005;12(1):63-69	

IV. i. Joerg Holste Exhibits (Continued)			
T-1201	2005	Klosterhalfen B, et al. "The lightweight and large porous mesh concept for hernia repair." Expert Rev Med Devices 2005;2(1): 1-15	
T-1202	March 1-13, 2006	Emails Re: AW: Mesh and Tissue Contraction in Animal, with Ethicon Scientific Statement on Shrinking Meshes and PowerPoint presentation attached	ETH.MESH.05446127-39
T-1203		Characteristics of Synthetic Materials Used in Prolapse and Incontinence Surgery, PowerPoint presentation	ETH.MESH.00838428-no Bates numbers
T-1204	October 2, 2003	ULTRAPRO Mesh Pricing Committee PowerPoint presentation	ETH.MESH.05483362-no Bates numbers
T-1205	September 25, 2012	Clinical Expert report of Piet Hinoul, MD, PhD	ETH.MESH.08315779-810
T-1206	November 2004	Berrocal J, et al. "Conceptual advances in the surgical management of genital prolapse: the TVM technique emergence." J Gynecol Obstet Biol Reprod 2004;33:577-587	ETH.MESH.00659678-90
T-1207		Projekt "Edelweiß" data	ETH.MESH.05718952-no Bates numbers
T-1208	M arch 11-April 23, 2005	Emails Re: Infection risk implantation TVT U	ETH.MESH.05549189-91
T-1209		Clinical Infection Risk Assessment for Gynecare TVT Universal (TVT U)	ETH.MESH.05505944-46
T-1210	April 2008	Interim report mesh explants pelvic floor repair, by Professor B. Klosterhalfen	ETH.MESH.00006636
T-1211	June 2009	Intermediate Report—Prolapse Mesh Explants by Professor Bernd Klosterhalfen, MD	ETH.MESH.02157879-80
T-1212	May 6, 2013	Infections/Inflammation of the Genituourinary Tract: Kidney and Bladder (II) poster: Shah K et al. "Bacteriological Analysis of Explanted Transvaginal Meshes."	

IV. i. Joerg Holste Exhibits (Continued)			
T-1213	2006	Harrell AG, et al. "In vitro infectability of prosthetic mesh by methicillin-resistant *Staphylococcus aureus*." Hernia 2006;10:120-124	
T-1214	2009	Vollebregt A, et al. "Bacterial colonization of collagen-coated polypropylene vaginal mesh: are additional intraoperative sterility procedures useful?" Int Urogynecol J 2009;20:1345-1351	
T-1215	2007	Rezapour M, et al. "A 3-month preclinical trial to assess the performance of a new TVT-like mesh (TVTx) in a sheep model." Int Urogynecol J 2007;18:183-187	
T-1216	December 20-21, 2004	Emails Re: AW: TVT-Next generation Questions	ETH.MESH.05245392-99
T-1217	2005	3-Month Sheep Study (SO04/2-2-1)	ETH.MESH.06403724-40
T-1218	October 26, 2005-January 3, 2006	Emails Re: Results of TVTx preclinical trial	ETH.MESH.05246116-22
T-1219		TVT Secur YTD Findings, PowerPoint slides	ETH.MESH.00840056-no Bates numbers
T-1220	February 28, 2006	Corporate Product Characterization Plan for Gynecare TVT S (Secur)	ETH.MESH.04939027-35
T-1221	November 28, 2005	Letter from FDA Re: K052401 (Gynecare TVT Secur System)	ETH.MESH.00019925-20019
T-1222	2010	Schumpelick V, et al. "Hernia Repair Sequelae."	
T-1223	2006	Meschia M, et al. "Tension-free vaginal tape (TVT) and intravaginal slingplasty (IVS) for stress urinary incontinence: A multicenter randomized trial." American Journal of Obstetrics and Gynecology 2006;195:1338-42	
T-1224	July 16, 2010	Letter Re: Preclinical Efficacy Assessment for ETHICON GYNECARE GYNEMESH M	ETH.MESH.04940233
T-1225	January 20, 2010	Emails Re: Tissue reaction ULTRAPRO, with Junge article attached	ETH.MESH.05127423-30

IV. j.	**Martin Weisberg Exhibits**		
Exhibit #	**Date**	**Description**	**Bates #**
T-311		CV of Martin Weisberg, M.D.	
T-312	December 5, 2002	Email Re: Mulberry clinic & regulatory meeting	ETH.MESH.03801821-22
T-313	December 5, 2002	Email Re: Mulberry	ETH.MESH.03918324
T-314	December 5, 2002	Emails Re: Mulberry	ETH.MESH.03918325-26
T-315	December 5, 2002	Emails Re: Mulberry	ETH.MESH.03918327-28
T-316	December 5, 2002	Emails Re: Mulberry	ETH.MESH.03918329-31
T-317	December 5, 2002	Emails Re: Mulberry	ETH.MESH.03918332-34
T-318	December 5-6, 2002	Emails Re: Mulberry	ETH.MESH.03918335-37
T-319	January 6, 2003	Project Mulberry Preliminary Clinical Diligence Report	ETH.MESH.01815660-64
T-320	March 4-25, 2003	Emails Re: Mulberry	ETH.MESH.03934876-79
T-321	April 8, 2003	Emails Re: Project Mulberry	ETH.MESH.00865216-17
T-322	April 1-8, 2003	Emails Re: Trans-obturator approach/Clinical evidence	ETH.MESH.00865220-21
T-323		High Level F/U's From Today's Meeting	ETH.MESH.00858080-81
T-324	April 13-14, 2003	Emails Re: Mulberry update	ETH.MESH.00260591-92
T-325	April 16, 2003	Emails Re: Mulberry/Clinical Data Pr de Leval/Safety	ETH.MESH.03918497
T-326	April 16, 2003	Emails Re: Draft report translated by "Babel fish" http://babelfish.altavista.com/tr	ETH.MESH.00865069-72
T-327	April 20, 2003	Email Re: mulberry clinical opinion	ETH.MESH.03801837
T-328		Martin Weisberg's clinical opinion of Gynecare TVT	ETH.MESH.03801838-46
T-329	April 30, 2003	Tension-free Vaginal Obturator Tape (TVOT) – April 30 2003 – Meeting report	ETH.MESH.03934952-67

IV. j.	**Martin Weisberg Exhibits (Continued)**		
T-330		Manuscript Draft of de Leval article, "Novel surgical technique for the treatment of female stress urinary incontinence: Transobturator Vaginal Tape Inside-Out"	ETH.MESH.00262089-123
T-331	2003	de Leval J "Novel Surgical Technique for the Treatment of Female Stress Urinary Incontinence: Transobturator Vaginal Tape Inside-Out." European Urology 2003;44:724-730	ETH.MESH.00259646-52
T-332	June 19, 2003	Email Re: Protocole [sic] TVT-O-001	ETH.MESH.03935061
T-333	June 19, 2003	Emails Re: Protocole [sic] TVT-O-001	ETH.MESH.01815567-68
T-334	June 24, 2003	Emails Re: Mulberry Clinical Study 3	ETH.MESH.01815607
T-335	July 16-17, 2003	Emails Re: Suggestions for a reply to the competent authority	ETH.MESH.03928540-42
T-336	December 16	Clinical Expert Report of Martin Weisberg, M.D. (Assessment of the "inside-out" Transobturator Approach to Implant a Prolene (Polypropylene) Mesh for the Treatment of Stress Urinary Incontinence in Females)	ETH.MESH.00259634-44
T-337		Gynecare TVT Obturator System Instructions for Use	ETH.MESH.02340829-35
T-338	May 12, 2004	Email Re: Dr. Disciullo	ETH.MESH.08002852
T-339	2004	Medwatch Report (Report # 2210968-2004-00289)	ETH.MESH.03589125-26
T-340	July 10, 2003	Emails Re: IFU Update	ETH.MESH.00261557-58
T-341	July 15-August 8, 2003	Emails Re: I: Transient Leg Pain with MULBERRY	ETH.MESH.03803462-65
T-342	December 18-19, 2003	Emails Re: Final Mulberry DDSA for signature	ETH.MESH.01808684-86
T-343	September 20, 2002	Clinical Expert Report: Gynemesh Prolene Soft (Polypropylene) Mesh	ETH.MESH.03737968-75
T-344	August 28, 2000	Email Re: Discussion with [Redacted]	ETH.MESH.03736578
T-345	December 2, 2005	Clinical Expert Report of Martin Weisberg, M.D.	ETH.MESH.04385229-45

IV. j.	**Martin Weisberg Exhibits (Continued)**		
T-346		Martin Weisberg's Application for Employment at Johnson and Johnson	ETH.MESH.08183517-20
T-347	May 22, 2001	Offer to Martin Weisberg to join Johnson and Johnson as Associate Director of Medical Affairs Dept.	ETH.MESH.08183624-26
T-348		Announcement of Martin Weisberg's appointment as Associate Director of Medical Affairs, Gynecare Products Division, effective June 11, 2001	ETH.MESH.08183622
T-349	September 15, 1998	New York Times article, "Death In Surgery Reveals Troubled Practice and Lax Hospital"	
T-350	March 2002	Ask Medical Affairs issue	ETH.MESH.03738509-10
T-351	June 5-July 9, 2003	Emails Re: TVT question	ETH.MESH.03715978-80
T-352	November 1, 2000	Memo Re: Complaint	ETH.MESH.03736932
T-353	September 20-October 13, 2002	Emails Re: Soft Prolene, with Martin Weisberg's Clinical Expert Report (with edits) attached	ETH.MESH.03910183-93
T-354	September 20-October 15, 2002	Emails Re: Soft Prolene	ETH.MESH.03910175-77
T-355	January 28, 1998	501k Summary – K974098 (Tension Free Vaginal Tape (TVT) System)	
T-356	1999	Kobashi KC et al. "Erosion of Woven Polyester Pubovaginal Sling." The Journal of Urology 1999;162:2070-2072	
T-357		Selected sections of 510k for Tension Free Vaginal Tape (TVT) System	ETH.MESH.00371547-94
T-358	July 20-September 15, 1999	Major Executive Committee Actions	ETH.MESH.04193990-93
T-359	June 7, 2002	Email Re: Dr. Alex Wang, Taiwan—Reports of "tape rejection" with TVT	ETH.MESH.00409674-75
T-360	August 2005	Consulting Agreement Requisition Form	ETH.MESH.02101709-19
T-361		7 Year Data Indicates Strong Continued Safety and Effectiveness for Gynecare TVT Tension-free Support for Incontinence	ETH.MESH.05794787-88

IV. j.	**Martin Weisberg Exhibits (Continued)**		
T-362	December 2004	Nilsson CG, et al. "Seven-Year Follow-up of the Tension-Free Vaginal Tape Procedure for Treatment of Urinary Incontinence." Obstet Gynecol 2004;104:1259-62	ETH.MESH.00999764-67
T-363	2004	Only Gynecare TVT Has Long-term Results You Can See…And Believe, patient brochure	ETH.MESH.00658058-65
T-364	November 18, 2003	Note to file Re: Mesh Fraying For TVT Devices	ETH.MESH.01126906-07
T-365	April 23-June 6, 2001	Emails Re: TVT recommendation from Dr. Alex Wang	ETH.MESH.03905472-77
T-366	February 27, 2004	Emails Re: Important: 2 TVT Complaints concerning allegedly brittle mesh	ETH.MESH.00863391-93
T-367	November 10, 2004	Letter from PD Dr. Eberhard Re: TVT blue tape	ETH.MESH.02180828-30
T-368	November 12, 2004	Emails Re: Mesh Fraying: Dr EBERHARD letter	ETH.MESH.02180826-27
T-369	October 18, 2004	Translation of PD Doctor Eberhard's letter of 18.10.04	ETH.MESH.02180833
T-370	November 18-21, 2005	Emails Re: !!!!!GREAT NEWS FOR TVT LASER CUT MESH!!!!!	ETH.MESH.00301741-42
T-371	May 9, 2006	Email Re: Particle loss on TVT	ETH.MESH.00585802
T-372	June 12, 2006	Emails Re: TVT LCM – particle loss (reimbursement submission)	ETH.MESH.00585842-43
T-373	2006	Hazell L, et al. "Under-Reporting of Adverse Drug Reactions: A Systematic Review." Drug Safety 2006;29(5):385-396	
T-374	November 16, 2005	Email Re: Updated TVT and TVT-O Complication Rates 11-15-05, with Complication Rate PowerPoint slides attached	ETH.MESH.00875647-48
T-375	August 19-September 6, 2003	Emails Re: TVT	ETH.MESH.03738466-67
T-376	November 16-29, 2005	Emails Re: Updated TVT and TVT-O Complication Rates 11-15-05	ETH.MESH.05560961-63
T-377		Martin Weisberg's Clinical Expert Report	

IV. j.	**Martin Weisberg Exhibits (Continued)**		
T-378	July 29-August 2, 2011	Emails Re: BSI Technical File Audit – July 28-29, 2011	ETH.MESH.00301367-69
T-379	2001	Freedom From Stress Urinary Incontinence, patient brochure	ETH.MESH.02619504-11
T-380	October 16, 2002	Copy Review Submission Form (TVT Patient Brochure Reprint)	ETH.MESH.00143758-59
T-381	February 6	Copy Review Submission Form (TVT Sales Aid)	ETH.MESH.00142628-30
T-382	2002	"5 Years of Proven Performance" Sales Aid	ETH.MESH.00339437-42
T-383	2002	"5 Years of Proven Performance" Sales Aid	ETH.MESH.00156152-57
T-384	November 9, 2005	Gynecare Copy Review Submission Form (Gynecare Prolift Patient Brochure)	ETH.MESH.00145991
T-385	2005	Pelvic Organ Prolapse patient brochure (not TVT)	ETH.MESH.04041579-86
T-386	February 20, 2001	Issue Report for TVT Retropubic (Tracking # 30001175)	ETH.MESH.02621661-64
T-387	May 11, 2001	Letter Re: TVT* Device (Reference: 30001175)	ETH.MESH.03482828
T-388	February 21, 2001	Issue Report for TVT Retropubic (Tracking # 30001177)	ETH.MESH.02621670-74
T-389	May 22, 2001	Issue Report for TVT Retropubic (Tracking # 30001377)	ETH.MESH.02621931-35
T-390	May 25, 2001	Issue Report for TVT Retropubic (Tracking # 30001382)	ETH.MESH.02621936-41
T-391	June 5, 2001	Issue Report for TVT Retropubic (Tracking # 30001414)	ETH.MESH.02621966-70
T-392	July 10, 2001	Issue Report for TVT Retropubic (Tracking # 30001483)	ETH.MESH.02622081-84
T-393	September 18, 2001	Issue Report for TVT Retropubic (Tracking # 30001634)	ETH.MESH.02622276-79
T-394	November 14, 2001	Issue Report for TVT Retropubic (Tracking # 30001732)	ETH.MESH.02622374-77
T-395	February 8, 2002	Issue Report for TVT Retropubic (Tracking # 30001917)	ETH.MESH.02622581-85
T-396	February 27, 2002	Issue Report for TVT Retropubic (Tracking # 30001947)	ETH.MESH.02622612-16
T-397	March 1, 2002	Issue Report for TVT Retropubic (Tracking # 30001959)	ETH.MESH.02622627-31
T-398	March 15, 2002	Issue Report for TVT Retropubic (Tracking # 30002004)	ETH.MESH.02622686-90

IV. j.	**Martin Weisberg Exhibits (Continued)**		
T-399	April 3, 2002	Issue Report for TVT Retropubic (Tracking # 30002042)	ETH.MESH.02622755-59
T-400	April 22, 2002	Issue Report for TVT Retropubic (Tracking # 30002075)	ETH.MESH.02622778-82
T-401	June 25, 2002	Issue Report for TVT Retropubic (Tracking # 30002622)	ETH.MESH.02625032-37
T-402	August 14, 2002	Issue Report for TVT Retropubic (Tracking # 30002760)	ETH.MESH.02623164-68
T-403	August 14, 2002	Issue Report for TVT Retropubic (Tracking # 30002759)	ETH.MESH.02623159-63
T-404	September 4, 2002	Issue Report for TVT Retropubic (Tracking # 30002826)	ETH.MESH.02623268-72
T-405	September 11, 2002	Issue Report for TVT Retropubic (Tracking # 30002844)	ETH.MESH.02623282-86
T-3115	2005	Gynecare TVT Secur System Instructions for Use	ETH.MESH.02340568-90
T-3116		Gynecare TVT Instructions for Use	ETH.MESH.00211510-15
T-3117	2005	Gynecare TVT Obturator System Tension-free Support for Incontinence Instructions for Use	ETH.MESH.03653529-36
T-3118	October 21, 2008	Email Re: Information about FDA notification on use of mesh in pelvic surgery, with FDA Public Health Notification to Healthcare professionals attached	ETH.MESH.02310653-57
T-3119	December 2, 2005	Clinical Expert Report of Martin Weisberg, M.D.	ETH.MESH.03714002-18
T-3120	August 30-September 15, 2005	Emails Re: clinical expert report	ETH.MESH.03905619-21
T-3121		Risk Management Report – TVT Secur System (Revision B-Development)	ETH.MESH.00752928-32
T-3122		Clinical Expert Report of Charlotte D. Owens	ETH.MESH.01037447-55
T-3123	October 3, 2005	A Pilot Study of the Gynecare TVT Secur System (Tension-free Support for Incontinence) For the Treatment of Stress Urinary Incontinence (Protocol 300-05-002)	ETH.MESH.00538202-42
T-3124		Traditional 510(k) Notification – Gynecare TVT Secur System: K052401	ETH.MESH.07876572-819
T-3125	March 23, 2010	Emails Re: Input to the one-pager to BR	ETH.MESH.00351439-41

IV. j.	**Martin Weisberg Exhibits (Continued)**		
T-3126		3-Month Sheep Study (SO04/2-2-1)	ETH.MESH.06403724-40
T-3127		Pictures of mesh implant	
T-3128	November 28-December 2, 2005	Emails Re: TVT SECUR Minutes – Team Meeting November 22nd 2005_Agenda November 29th 2005	ETH.MESH.00214524-29
T-3129	August 10, 2005	Gynecare TVT Secur Cadaver Protocol	ETH.MESH.03714172-80
T-3130	August 25, 2005	Cadaver Protocol/Competition Report	ETH.MESH.00403003-17
T-3131	January 3, 2012	Letter from FDA Re: Postmarket Surveillance (PS) Study: PS120095	ETH.MESH.02661121-24
T-3132		TVT-Secur Quality Board, PowerPoint presentation	ETH.MESH.00874445-76
T-3133	May 29, 2012	Ethicon Inc. Background Information on Gynecare Pelvic Floor Repair Products and Gynecare TVT Secure	ETH.MESH.05600916-23
T-3134		Our Credo	
T-3135	September 5-6, 2003	Emails Re: TVT Response for Peggy Norton, M.D.	ETH.MESH.03738468-70
T-3136	April 13, 2005	Material Safety Data Sheet (Product Name: C4001 Polypropylene Homopolymer)	ETH.MESH.02026591-95
T-3137	January 28, 2004	Material Safety Data Sheet (Product: Marlex Polypropylenes (All Grades))	
IV. k.	**Piet Hinoul Exhibits**		
Exhibit #	**Date**	**Description**	**Bates #**
T-709	2003	Robinson D, et al. "What women want – Their interpretation of the concept of cure." Journal of Pelvic Medicine & Surgery 2003;9(6):273-277. (Abstract only)	
T-710	June 5-6, 2006	Emails Re: candidature	ETH.MESH.02900613-15
T-711	January 20-21, 2010	Emails Re: PROSIMA implant dimensions	ETH.MESH.00851319-21
T-712	2001	Freedom From Stress Urinary Incontinence, patient brochure	ETH.MESH.08003173-80
T-713	April 8, 2009	Emails Re: registry for all!	ETH.MESH.00591127-28

IV. k.	**Piet Hinoul Exhibits (Continued)**		
T-714	April 2011	Author reprint: Hinoul P, et al. "A Randomized, Controlled Trial Comparing an Innovative Single Incision Sling With an Established Transobturator Sling to Treat Female Stress Urinary Incontinence." The Journal of Urology 2011;185:1-7	ETH.MESH.00576529-40
T-715		Robinson D, et al. "What Women Want – Their Interpretation of the Concept of Cure." (Abstract only)	
T-716	September 9, 2011	CDRH Medical Devices Advisory Committee: Obstetrics and Gynecology Medical Devices Panel	
T-717	September 6, 2008	LIGHTning, PowerPoint slides	
T-718		Hinoul P, et al. "Transvaginal mesh repair using a light-weight, partially resorbable synthetic mesh kit: interim 3 month results." (Abstract only)	ETH.MESH.00017430-46
T-719	2011	Milani AL, et al. "Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes." Am J Obstet Gynecol 2011;204: 74.e1-8	
T-720		Various abstracts from Int Urogynecol J 2012;23(Suppl 2):S128-29	
T-721	June 27, 2012	Benefit Risk Profile of Transvaginal Mesh Products Used for the Treatment of Pelvic Organ Prolapse	ETH.MESH.06836620-57
T-722	September 25, 2012	Clinical Expert Report of Piet Hinoul, MD, PhD	ETH.MESH.08315779-810
T-723	October 21, 2008	Email Re: Information about FDA notification on use of mesh in pelvic surgery, with FDA's Public Health Notification to Healthcare professionals attached	ETH.MESH.02310653-57
T-724		Clinical Expert Report of Martin Weisberg, M.D.	ETH.MESH.03905059-72
T-725		Picture of mesh implant	
T-726		Picture of blue tape	

IV. k. Piet Hinoul Exhibits (Continued)			
T-727	2010	Hinoul P, et al. "Factors determining the adoption of innovative needle suspension techniques with mesh to treat urogenital prolapse: a conjoint analysis study." European Journal of Obstetrics & Gynecology and Reproductive Biology 2010	ETH.MESH.02132924-28
T-728	January 2010	Ethicon Women's Health and Urology Brand Equity Study – Final Report	ETH.MESH.03643186-no Bates numbers
T-729		Gynecare TVT Secur Project Overview – PLT Review (Stage: Post-Launch Assessment/Close-Out)	ETH.MESH.00826057-67
T-730	January 3, 2012	Letter from FDA Re: Postmarket Surveillance (PS) Study: PS120095 (Trade Name: GYNECARE TVT SECUR SYSTEM) – K052401	ETH.MESH.02661121-24
T-731	May 29, 2012	Background Information on Gynecare Pelvic Floor Repair Products and Gynecare TVT Secure	ETH.MESH.05600916-23
T-732	June 2012	Clinical Study Report: Evaluation of the TVT Secur System for Stress Urinary Incontinence (Study Code 300-05-002)	ETH.MESH.06479808-85
T-733	May 18, 2011	Investigating Mesh Erosion in Pelvic Floor Repair, PowerPoint presentation	ETH.MESH.02589032-79
IV. l. Susan Lin Exhibits			
Exhibit #	**Date**	**Description**	**Bates #**
T-156		"Stress Urinary Incontinence in Women" patient brochure	ETH.MESH.02619601-16
T-157	August 10, 2012	Approval of Advertising and Promotional Materials for Medical Devices and Combination Products (Revision 8)	ETH.MESH.07983955-72
T-158		Title 15—Commerce and Trade § 51, pages 52-56	
T-159		"Breaking the Ice About SUI" patient brochure	
T-160		"The Choice to End Stress Urinary Incontinence" patient brochure	ETH.MESH.00166617-32
T-161		"The Choice to End Stress Urinary Incontinence" patient brochure	ETH.MESH.00163644-59
T-162		"Treatment Options for Stress Urinary Incontinence" brochure	ETH.MESH.00161969

IV. l.	**Susan Lin Exhibits (Continued)**		
T-163		"Treatment Options for Stress Urinary Incontinence" brochure in Spanish	
T-164, T-2056		"Treatment Options for Stress Urinary Incontinence" promotional material	ETH.MESH.02236180-87
T-165		Company Procedure for US Regulatory Affairs Review of Promotion and Advertising Material for Medical Devices (Revision 1)	ETH.MESH.08164278-86
T-166		Company Procedure for US Regulatory Affairs Review of Promotion and Advertising Material for Medical Devices (Revision 1)	ETH.MESH.03667696-704
T-167	January 8-14, 2009	Emails Re: Revised TVT CR #2008-1359	ETH.MESH.00345328-29
T-169	September 29-October 1, 2008	Emails Re: EPI & Fair Balance status? With Patient EPI attached	ETH.MESH.05181555-58
T-170	May 6, 2011	Email Re: EPI	ETH.MESH.07456394
T-172		Standard Operating Procedure – Corporate Communications Department: Copy Review Process	ETH.MESH.06034548-55
T-173		Standard Operating Procedure—Copy Review Process (Revision 2)	
T-174		Standard Operating Procedure—Process for the Review and Approval of Promotional and Advertising Material for Medical Devices and Combination Products (Revision 3)	ETH.MESH.03456681-96
T-175		Standard Operating Procedure—Process for the Review and Approval of Promotional and Advertising Material for Medical Devices and Combination Products (Copy Review) (Revision 4)	ETH.MESH.00983775-92
T-176		Operating Procedure for the Review and Approval of Advertising and Promotional Materials for Medical Devices and Combination Products (Copy Review/Approval) (Revision 5)	ETH.MESH.00093575-88
T-177		Operating Procedure for the Review and Approval of Advertising and Promotional Materials for Medical Devices and Combination Products (Copy Review/Approval) (Revision 6)	ETH.MESH.03475340-54

IV. l.	**Susan Lin Exhibits (Continued)**		
T-178		Operating Procedure for the Review and Approval of Advertising and Promotional Materials for Medical Devices and Combination Products (Copy Approval) (Revision 7)	
T-179	1999-2011	In Re: Pelvic Mesh/Gynecare Litigation – TVT/SUI Patient Brochures chart	
T-180	April 24-May 3, 2013	Emails Re: Production of Policy before Ms. Lin's deposition	
T-181	January 28, 1998	510k Notification – K974098 (Tension Free Vaginal Tape (TVT) System)	
T-3040		Notice to Take Oral Deposition of Defendant Through Designated Witness, Susan Lin	
T-3041	2005	510k Notification – K052401 (Gynecare TVT Secur System)	ETH.MESH.07876572-819
T-3042	March 23, 2010	Emails Re: Input to the one-pager to BR	ETH.MESH.00351439-41
T-3043	August 14-September 16, 2009	Emails Re: Question for TVT-O	ETH.MESH.00345813-15
T-3044	2005	A 3 month pre-clinical trial to assess the fixation force of a new TVT (TVTx) in the sheep model – Study No. SO04/2-2-1	ETH.MESH.06403724-40
T-3045	November 28-December 2, 2005	Emails Re: TVT SECUR Minutes – Team Meeting November 22nd 2005_Agenda November 29th 2005	ETH.MESH.00214524-29
T-3046	June 2012	Clinical Study Report: Evaluation of the TVT Secur System for Stress Urinary Incontinence (Study code 300-05-002)	ETH.MESH.06479808-85
T-3047	October 8, 2002	Regulatory Strategy—United States	ETH.MESH.07780957-89
T-3048	2005	Gynecare TVT Secur System Instructions for Use (IFU)	ETH.MESH.02340568-755
T-3049	January 29, 2007	2006 Performance and Development Plan Summary for Yiqun Lin	
T-3050	January 31, 2008	2007 Performance and Development Plan Summary for Yiqun Lin	

IV. l.	**Susan Lin Exhibits (Continued)**		
T-3051	October 21, 2008	FDA Notification About Use of Surgical Mesh to Treat Pelvic Organ Prolapse and Stress Urinary Incontinence – Standby for Media/Analyst Inquiries	ETH.MESH.00350879-81
T-3052		FDA Notification to Healthcare Professionals About Serious Complications Associated with Surgical Mesh for Prolapse and Incontinence	ETH.MESH.03653779-80
T-3053	2010	Wall LL, et al. "The perils of commercially driven surgical innovation." Am J Obstet Gynecol 2010;202: 30.e1-4	ETH.MESH.03361364-67
T-3054	August 8-14, 2008	Emails Re: Rational for Reclassification of TVT-SECUR	ETH.MESH.03653311
T-3055		Rational for Changing EU Classification of TVT-SECUR SYSTEM, prepared by Susan Lin	ETH.MESH.03653305-07
T-3056	June 24, 2008	Project: Scion, "TVT-SECUR mass distribution measurement: Follow up for 50% rule"	ETH.MESH.03653312-13
T-3057	May 20-21, 2010	Emails Re: TVT tech files – Post-Market Surv	ETH.MESH.03654151

V. Issue Reports		
Date	**Description**	**Bates #**
1999-2000	Issue Reports TVT Retropubic 1999-2000	ETH.MESH.02620465-73, 490-493, 556-559, 593-596, 686-690, 705-709, 909-922, 964-968, 1142-1146,1147-1158, 1179-1183, 1288-1295, 1453-1456, 1462-1466
2001-2002	Issue Reports TVT Retropubic 2001-2002	ETH.MESH.02622276-79, 1596-99, 1661-64, 1670-74, 1834-39, 1931-40, 1966-70, 2043-46, 2081-84, 2267-71, 2374-77, 2420-23, 2556-59, 2581-85, 2600-03, 2612-16, 2627-31, 2686-95, 2725-28, 2755-59, 2778-82, 2891-94, 3003-07, 3139-43, 3159-63, 3164-68, 3207-10, 3250-54, 3268-72, 3283-36, 3355-58, 3406-10, 3442-46, 3462-65, 3497-505, 3516-21, 3558-62, 3595-99, 3646-50, 3714-3719, 3743-47, 5032-37, 51570-74
2003	Issue Reports TVT Retropubic 2003	ETH.MESH.02625074-95, 5120-29, 5150-54, 5159-63, 5185-88, 5246-49, 5267-70, 5316-20, 5397-403, 5453-57, 5497-501, 5669-88, 5710-30, 5737-47, 5752-57, 5826-31, 5869-73, 5889-94, 5959-63, 6015-19, 6049-55, 6075-85, 6092-96, 6137-42, 6309-14, 6369-73
2004	Issue Reports TVT Retropubic 2004	ETH.MESH.0262 6387-91, 6430-34, 6493-96, 6533-52, 6558-62, 6678-82, 6821-25, 6864-68, 6940-43, 6960-65, 7023-28, 7074-81, 7096-100, 7130-50, 7156-65, 7177-88, 7204-19, 7224-29, 7242-47, 7294-99
2005-2007	Issue Reports TVT Retropubic 2005-2007	ETH.MESH.02627331-8697
2008-2009	Issue Reports TVT Retropubic 2008-2009	ETH.MESH.02628698-30133
2010-2011	Issue Reports TVT Retropubic 2010-2011	ETH.MESH.02630134-2004

VI. Documents	
Description	**Bates # (Exhibit #)**
TOMUS-Trial of Mid-Urethral Slings (Sponsor: New England Research Institutes)	
Investigator Initiated Study Process, PowerPoint presentation by Kimberly Hunsicker	
New Study Shows Minimally Invasive Surgery for Female Incontinence Offers Good Long-Term Cure Rates	ETH.MESH.00155598-600
"Innovative Surgical Alternative for the Treatment of Female Stress Urinary Incontinence"	ETH.MESH.00161444-45 (Ex. 14-Fights)
Communication Plan to Close TVT WORLD Registry	ETH. M ESH.00533283-86 (Ex. 692)
"In Stress Urinary Incontinence: Consistent Results. Reliable Outcomes" brochure	ETH.MESH.00169748-51 (Ex. 11-Fights)
"30 minutes can make a difference in your life" promotional material	ETH.MESH.00162423-24
Nilsson CGN, et al. "7 Years Follo-Up [sic] of the Tension-Free Vaginal Tape (TVT) Procedure."	ETH.MESH.00162425
Proprietary Data for the Gynecare TVT Family of Products	ETH.MESH.00339054-57
Stop Coping. Start Living. Treatment Options for Urinary Incontinence, PowerPoint presentation	(Ex. T-997)
LCM project Photographs Comparing Laser Cut Mesh vs Mechanical Cut Mesh	ETH.MESH.06001408
Second half of photo presentation, re: Degradation	ETH.MESH.00584527
Dependability – Gynecare TVT Family of Products (Tension-free Support for Incontinence)	ETH.MESH.00658430-31 ETH.MESH.02237103-04 (Ex. 10-Fights)
Various Sections of 510k for Tension Free Vaginal Tape (TVT) System	ETH.MESH.00371547-56 (Ex. T-357)
Wang et al. "Tension-Free Vaginal Tape (TVT) for Urinary Stress Incontinence—A Preliminary Report"	ETH.MESH.00371572-86
Second Generation TVT	ETH.MESH.03907468-69 (Ex. T-843)
Clinical Expert Report: Prolene Soft (Polypropylene) Mesh	ETH.MESH.03910186-93
Hellhammer et al. "Shrinking Meshes?"	ETH.MESH.05446129-32
Female Urinary Incontinence-A Primary Care Perspective, PowerPoint presentation	
Timeline of Hernia Mesh Development and Incontinence (TVT) Development	ETH.MESH.01816990-no Bates numbers (Ex. T-1229)
Make Data and Safety Your Choice, Gynecare Family of Products info	ETH.MESH.00339053-57 (Ex. D. Mahar 1)

VI. Documents (Continued)		
Letter Re: Summary of Findings and Next Steps from 10.12/01 TVT DTC Focus Groups		ETH.MESH.01217285-88
Cancellation Agreement		ETH.MESH.08692670-72
Tension-free Vaginal Tape (TVT) System Indications, Contraindications, Warnings and Precaustions, and Adverse Reactions		ETH.MESH.00158636
Chronic Pain Prevention/future-Bioengineer's point of view, PowerPoint presentation		ETH.MESH.05916450-no Bates (Ex. T-1238)
The (clinical) argument of lightweight mesh in abdominal surgery, PowerPoint presentation		
7 Year Data Indicates Strong Continued Safety and Effectiveness for Gynecare TVT Tension-free Support for Incontinence		ETH.MESH.00524444-45
Consulting and Technology Agreement		ETH.MESH.08696050-55
Ethicon, Inc. Worldwide Complaint Reporting Statement		
Untitled GYNECARE TVT PowerPoint presentation		ETH.MESH.00525322-400
License and Supply Agreement		ETH.MESH.08696084-134 (Ex. T-880), also ETH.MESH.09746948-98
Memo Re: Mechanical Cut vs. Laser Cut Mesh Rationale		ETH.MESH.00858252-253
The Science of "What's Left Behind"… Evidence & Follow-Up of Mesh Use for SUI, PowerPoint Presentation by Doug H. Grier, Sound Urological Associates, PS		
GYNECARE TVT Tension-free Support for Incontinence, PowerPoint slides with notes		ETH.MESH.05793690-93
Professional Education Program		ETH.MESH.00158559-90
Memo Re: Dr. Donnica Moore Opportunity Analysis and Recommendation		ETH.MESH.00766347-49 (Ex. T-3030)
Data showing PRF, CH and UH Rankings		ETH.MESH00669604
Project Tomel Due Diligence Summary		ETH.MESH.09748308-85
Consulting Agreement between Ethicon and Contape		ETH.MESH.08692673-93
Accurate HCP Report (inclusive of all contracts with end dates in 2009)		ETH.MESH.0176065
Memo: VOC on new Laser Cut TVT Mesh		ETH.MESH.01809082-83
TVT-2 Analysis		ETH.MESH.01317515-24
Gynecare TVT, PowerPoint presentation with notes		ETH.MESH.00159636-719
AE and complication of the Slings, Meeting Agenda		ETH.MESH.04081189-90
Date	**Description**	**Bates # (Exhibit #)**
January 27-29	Gynecare TVT and Thermachoice Patient Advertising	ETH.MESH.00766975-76
December 1	Biocompatibility of Meshes	ETH.MESH.05446133-39
March 8, 1991	Device Labeling Guidance #G91-1 (blue book memo)	(Ex. T-16)

VI. Documents (Continued)		
1996	Ulmsten et al. "An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence" The International Urogynecology Journal 1996; 7:81-86	ETH.MESH.05795664-69 (Ex. 879)
March 20, 1997	Medscand Medical Validation Fact Book – Heat Sealer HSE-3	ETH.MESH.01317564-613
October 17, 1997	Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure (Clinical Report)	ETH.MESH.00371587-94
1998	Ulmsten et al. "A Multicenter Study of Tension-Free Vaginal Tape (TVT) for Surgical Treatment of Stress Urinary Incontinence" Int Urogynecol J 1998;9:210-213	ETH.MESH.00145084-88
January 28, 1998	510k Summary of Safety and Effectiveness – K974098	(Ex. T-355)
January 28, 1998	510(k) Substantial Equivalence letter with 510(k) Notification – K974098	ETH.MESH.00371496-594 (Ex. T-11)
March 17, 1998	Ethicon LTD Clinical Research and Development, TVT for GSI Surgery Investigator Brochure, A Prospective Randomized Comparative Trial of a Tension-Free Vaginal Tape (TVT) Vs. Burch Culposuspension for 'Primary' Genuine Stress Incontinence CT-TVT-001-97	ETH.MESH.04447108-63
April 1999	Ulmsten et al. "A three-year follow up of tension free vaginal tape for surgical treatment of female stress urinary incontinence" British Journal of Obstetrics and Gynaecology 1999; 106:345-350	ETH.MESH.00158629-36
November 1999	University of Uppsala Acknowledgement	ETH.MESH.08692694-96
November 15, 1999	Emails Re: AW: Cordozo Trial, some redacted material	ETH.MESH.08167644-45
November 24-28, 1999	Emails Re: TVT event	ETH.MESH.03917309-12 (Ex. 839)
December 15, 1999	Emails Re: TVT Blue – feedback from Carl Gustaff Nilsson	ETH.MESH.06694812-13
2000	Expert opinion on the use of GYNECARE TVT Tension-Free Support for Incontinence: A Report of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases	ETH.MESH.00658177-98
April 17, 2000	Gynecare TVT Tension-free Support for Incontinence (No. 1728)	ETH.MESH.05529274-75
July 20-August 21, 2000	Emails Re: Pelvic floor repair Procedural Strategy	ETH.MESH.03909708-13

VI. Documents (Continued)		
September 22, 2000	Letter Re: "A three-year follow up of tension free vaginal tape for surgical treatment of female stress urinary incontinence" Article (TVT015)—Review for Reprint	ETH.MESH.00143697-99
September 22, 2000	"A Multicenter Study of Tension-Free Vaginal Tape (TVT) for Surgical Treatment of Stress Urinary Incontinence" Article (TVT005) – Review for Reprint	ETH.MESH.00143700-02
October 2000	TVT Update: Success & Complications (Causes and Recommendations)	ETH.MESH.04044797-800
November 29-30, 2000	Emails Re: Problem Statements for TVT Brainstorming Meeting	ETH.MESH.05529653
2001	Nilsson CG, et al. "Long-term Results of the Tension-Free Vaginal Tape (TVT) Procedure for Surgical Treatment of Female Stress Urinary Incontinence." Int Urogynecol J 2001;Suppl 2:S5-S8	ETH.MESH.00159481-84
April 11, 2001	Gynecare TVT Tension-free Support for Incontinence Competitive Mesh Products – Product Pointer	ETH.MESH.00161129-30
April 17, 2001	Product Pointer: "GYNECARE TVT Tension-free Support for Incontinence: A Synthetic Sling with Erosion Rates No Higher Than Autologous Slings"	ETH.MESH.00161131-32
June 18, 2001	2002-2003 US Marketing Plan for Gynecare TVT Tension-free Support for Incontinence	ETH.MESH.08798099-110, ETH.MESH.00162420-25
June 22, 2001	Scientific Advisory Panel on Pelvic Floor Repair, Preliminary Minutes (Chicago, IL)	ETH.MESH.02089392-99
July 2001	GYNECARE TVT Tension-free Support for Incontinence – Sales Force Update @ Divisional Meetings	ETH.MESH.00144304-31
July 2001	Incontinence/Pelvic Floor Management – GYNECARE TVT Tension-free Support for Incontinence, 2001 Marketing Plan	ETH.MESH.01137272-93 (Ex. T-200)
September 28, 2001	2002 US Marketing Plan for GYNECARE TVT Tension-free Support for Incontinence	ETH.MESH.09306899-910
October 2001	New Products Development – Gynecare Products	ETH.MESH.03909721-33 (Ex. 1038)
October 26, 2001	510(k) – K012628 (GYNECARE Tension-Free Vaginal Tape (TVT) Blue System)	ETH.MESH.00748310-450 (Ex. T-14)
March 28, 2002	Letter Re: 2001 sales performance of GYNECARE Worldwide Division of Ethicon, Inc.	ETH.MESH.08695896

VI. Documents (Continued)		
April 25, 2002	Device Design Safety Assessment (DDSA) Re-Evaluation for TVT	ETH.MESH.01317510-14
June 6-7, 2002	Emails Re: Friday June 7 Conference Call	ETH.MESH.03735432-33
June 7, 2002	Emails Re: Dr. Alex Wang, Taiwan—Reports of "tape rejection" with TVT	ETH.MESH.00409674-75 (Ex. T-359)
June 10, 2002	Emails Re: [REDACTED] Reports of "tape rejection" with TVT	ETH.MESH.03483690-93`
October 4, 2002	Rejection of Polypropylene Tape After the Tension-free Vaginal Tape (TVT) Procedure by Alex C. Wang, MD	ETH.MESH.00409657-58
September 20-October 13, 2002	Emails Re: Soft Prolene	ETH.MESH.03910183-85 (Ex. T-353)
September 20-October 15, 2002	Emails Re: Soft Prolene	ETH.MESH.03910175-77 (Ex. 354)
October 29-November 11, 2002	Emails Re: Dr. Wang's proposal	ETH.MESH.08793207-10
December 3, 2002	Emails Re: Prolene Rejection	ETH.MESH.00409670
December 27, 2002	Customer Initiated Research Grant Request	ETH.MESH.00409659-63
2003	Robinson et al. "What women want—Their interpretation of the concept of cure" Journal of Pelvic Medicine & Surgery 2003;9.6:273-277 (Abstract only)	(Ex. 709)
January 2003	Hilton et al. "Postural perineal pain associated with perforation of the lower urinary tract due to insertion of a tension-free vaginal tape" BJOG: an International Journal of Obstetrics and Gynaecology 2003;110:79-82	
March 20, 2003	Strategic Plan Challenge	ETH.MESH.04205632-36
May 13, 2003	Letter Re: GYNECARE TVT Physician Training Policy	ETH.MESH.00030098 (Ex. T-185)
June 11, 2003	Email Re: Stressful Secrets press release crosses wire	ETH.MESH.00764215-16 (Ex. 3032)
June 27-July 7, 2003	Emails Re: "Urethral erosion may occur with any sling material" Article (TVT063)	ETH.MESH.00030372-73 (Ex. T-3014)
October 23, 2003	Design Input Strategy – Project Mulberry (Gynecare TVT Obturator)	ETH.MESH.00259269-74
October 30, 2003	TVT Patent Portfolio	ETH.MESH.05236223-55
November 18, 2003	Note to file Re: Mesh Fraying For TVT Devices	ETH.MESH.00541379-80 (Ex. T-531)
2004	Only Gynecare TVT Has Long-term Results You Can See…and Believe, promotional brochure	ETH.MESH.00658058-65

VI. Documents (Continued)		
2004	2004 Performance and Development Plan Summary for Patricia Hojnoski	ETH.MESH.07931874-86 (Ex. T-69)
March 2, 2004	Emails Re: Reminder on BLUE mesh!	ETH.MESH.00865322-23
March 9, 2004	Emails Re: Complaint TVTO	ETH.MESH.00863405-07
September 2004	Professional Education for GYNECARE TVT Physician Training	ETH.MESH.03624321-22 (T-184)
September 7-16, 2004	Emails Re: Ongoing TVT-O Action Items	ETH.MESH.00864503-07
November 1, 2004	Emails Re: Update from the Oct27 cadaver lab	ETH.MESH.05548122-23
January 3, 2005	2005 Variable Compensation Plan – Sales Representative	ETH.MESH.05768705-12 (Ex. T-1044)
February 1, 2005	TVT Bonnie Blair Campaign-Professional Advertising Initiatives, PowerPoint presentation	
August 29, 2005	Establishment Inspection Report, including related forms and CAPAs	ETH.MESH.07281423-922
October 12, 2005	Letter Re: 810041B TVT Device, Blue Mesh (Reference #6167, our file #30005383)	ETH.MESH.03535750
November 14, 2005	K033568 Special 510(k) Modified Gynecare TVT Obturator System	ETH.MESH.07876926-7006
November 18-21, 2005	Emails Re: !!!!!GREAT NEWS FOR TVT LASER CUT MESH!!!!!	ETH.MESH.00301741-42
2006	The Gynecare TVT family of products for SUI – Marketing Services brochure	ETH.MESH.00161512-13 (Ex. T-542)
January 13-15, 2006	Emails Re: GYNECARE TVT Latest Complication Data	ETH.MESH.00134498-99
January 20, 2006	Emails Re: TVT U Completion Report Version 3	ETH.MESH.01218594-96
March 1-13, 2006	Emails RE: AW: Mesh and Tissue Contraction in Animal	ETH.MESH.05446127-28 (Ex. T-1231)
March 30, 2006	Emails Re: Laser Cut Mesh Positioning	ETH.MESH.00700348-50
March 30, 2006	Emails Re: TVT laser cut equivalency	ETH.MESH.01945854
April 18, 2006	Clinical Expert Report Laser Cut Mesh for Gynecare TVT Tension-free Support for Incontinence, Gynecare TVT Tension-free Support for Incontinence with Abdominal Guides, Gynecare TVT Obturator System Tension-free Support for Incontinence	ETH.MESH.00167104-10
June 26, 2006	Product Pointer Gynecare TVT Tension-free Support for Incontinence	ETH.MESH.00167119
July 20, 2006	Emails Re: TVT dataMcNelis, Linda, some Redacted material	ETH.MESH.00311802-04
October 9, 2006	Emails Re: TVT 10 year anniversary/10 year data from Nillson	ETH.MESH.00524059-60

VI. Documents (Continued)		
November 20, 2006	Sunoco Material Safety Data Sheet for C4001 Polypropylene	
December 22, 2006	Emails Re: Contact at Lifescan who ran the BB King campaign	ETH.MESH.08345895
2007	Gynecare TVT Secur Competitive Product Update 2007, PowerPoint presentation	
March 20, 2007	TVT-World-wide Observational Registry for Long-Term Data (Protocol 300-06-006)	ETH.MESH.00539862-98 (Ex. 689)
July 20, 2007	Email Re: Defining light weight mesh	ETH.MESH.05920616-17 (Ex. T-1227)
November 2007	FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology	(Ex. T-68)
February 8, 2008	Master Consulting Agreement	ETH.MESH.08692660-67
September 5, 2008	Marketing Services Release: New Study Offers More Than A Decade Of Evidence For Minimally-Invasive Surgery To Treat Female Incontinence	ETH.MESH.03459211-12
October 2008.	Ulatowski TA. Risk Management: A Regulatory Perspective, Presentation, Beijing	
October 20, 2008	FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence	ETH.MESH.02310655-57
October 22, 2008	Emails Re: Information about FDA notification on use of mesh in pelvic surgery	ETH.MESH.07937824-25
December 10-17, 2008	Emails Re: Updated Fair Balance for TVT Brochure	ETH.MESH.00772231-32
December 11, 2008	Emails Re: TVT 11 Year E-blast results (1st Round)	ETH.MESH.05183409-10
December 17, 2008	Emails Re: 2008 Budget Spend	ETH.MESH.00772228-29
December 18, 2008	Emails Re: TVT Patient Brochure Fair Balance/EPI Changes	ETH.MESH.00339083-84
2009	Grants, Sponsorships, and Other Support chart	
January 28, 2009	Email Re: TVT WORLD AE Report, with report attached	ETH.MESH.07181044-no Bates (Ex. T-691)
January 28, 2009	Emails Re: TVT WORLD AE Report	ETH.MESH.03208548-49 (Ex. T-690)
January 29, 2009	Emails Re: TVT IFUs on tape extrusion, exposure and erosion	ETH.MESH.04093125, ETH.MESH.04093117-18
February 2009	TVT World Registry, Maximizing the Investment, PowerPoint presentation	

VI. Documents (Continued)		
February 25, 2009	Email Re: Quick Response Needed to Finalize TVT WORLD Recommendation for Board Meeting on Monday Mar 2nd	ETH.MESH.03208738-39 (Ex. 696)
March 6, 2009	Emails Re: Fast Break Update	ETH.MESH.03966039-40 (Ex. T-208)
April 28, 2009	TVT-World-Wide Observational Registry for Long-Term Data (Protocol 300-06-006), Protocol Amendment 2	ETH.MESH.00533250-56 (Ex. T-694)
January 26-May 26, 2009	Emails Re: TVT Complications Statement 2008	ETH.MESH.02122903-07 (Ex. 978)
July 1, 2009	Code of Ethics on Interactions with Health Care Professionals Adopted by the Advanced Medical Technology Association	ETH.MESH.00139845-67
July 21-30, 2009	Emails Re: URGENT: TVT Japanese Package Insert	
2010	Dear Doctor Letter Re: Gynecare TVT Template	ETH.MESH.02236784-85
2010	Grants, Sponsorships, and Other Support chart	
January 8, 2010	Global Regulatory Strategy for TVT IFU (RMC P155060/E) Update	ETH.MESH.00340990-98
February 2010	Gynecare TVT Device Instructions for Use Revision	ETH.MESH.00340839
March 9-10, 2010	Emails Re: Scion PA commercial recommendation	ETH.MESH.00607406-10
2011	Grants, Sponsorships, and Other Support chart	
March 2011	Ethicon Polypropylene Mesh Technology, PowerPoint presentation	(Ex. T-1233)
March 29-31, 2011	Emails Re: Workshop on Vaginal Tape, with attachment: Paul Abrams report	ETH.MESH.07236294-97 (Ex. T-700)
September 8-9, 2011	FDA Executive Summary. Surgical mesh for treatment of women with pelvic organ prolapse and stress urinary incontinence. Obstetrics & Gynecology Devices Advisory Committee Meeting	
2012	Grants, Sponsorships, and Other Support chart	
May 11, 2012	Curriculum Vitae of Thomas A. Barbolt, PhD, DABT, 1981-2011, some redacted material	(Ex. P-1141)
July 26, 2012	Email Re: no subject, with attachment: Wall et al. "The perils of commercially driven surgical innovation" American Journal of Obstetrics & Gynecology 2009;201:1.e1-1.e4	ETH.MESH.05125293-97 (Ex. T-697)

VII. Patient Brochures and Instructions for Use (Not Included in Exhibits)		
Date	**Description**	**Bates # (Exhibit #)**
2000	Patient Brochure: Freedom from Stress Urinary Incontinence. It's within Your Control. with annotations	ETH.MESH.00144270-78 ETH.MESH.00160615-23
February 2000	Instructions for Use (IFU): TVT Tension-free Vaginal Tape	ETH.MESH. 05225354-85
August 2001	Instructions for Use (IFU): Gynecare TVT Tension-free Vaginal Tape	ETH.MESH. 02340306-69
2004	Patient Brochure: Stress Urinary Incontinence in Women What YOU Can do about it	ETH.MESH.08003181-96
October 2004	Instructions for Use (IFU): Gynecare TVT Tension-free Vaginal Tape	ETH.MESH. 02340471-503; ETH.MESH. 05222673-704
2005	Patient Brochure: Stress Urinary Incontinence in Women What YOU Can do about it	ETH.MESH.08003197-212 (Ex. 2053) ETH.MESH.00658421-29
2006	Patient Brochure: The Choice to end Stress Urinary Incontinence Find out how to stop urine leakage like Bonnie did	ETH.MESH.08003231-46
December 18, 2006	Patient Brochure: One day you have urine leakage. The next day you don't. End of story	ETH.MESH.03460640
2007	Patient Brochure: The Choice to end Stress Urinary Incontinence Find out how to stop urine leakage like Bonnie did	ETH.MESH.08003247 - 62 (Ex. 2080)
2008	Patient Brochure: Treatment Options for Stress Urinary Incontinence Stop coping. Start living.	ETH.MESH.08003279-94
2008	Patient Brochure: The Choice to End Stress Urinary Incontinence Find out how to stop urine leakage like Bonnie did, with annotations	ETH.MESH.03459088-104
2009	Instructions for Use (IFU): Gynecare TVT Tension-free Support for Incontinence	ETH.MESH. 03427878-945
2009	Patient Brochure: Treatment Options for Stress Urinary Incontinence Stop coping. Start living.	ETH.MESH.08003303-18, also without Bates #
2010	Patient Brochure: Stress Urinary Incontinence Stop coping. Start living.	ETH.MESH.06087471-72
2010	Patient Brochure: Gynecare TVT Tension-free Support for Incontinence	ETH.MESH.06087513-14
2011	Patient Brochure: Treatment Options for Stress Urinary Incontinence Stop coping. Start living.	ETH.MESH.08003295-02
2012	Patient Brochure: Treatment Options for Stress Urinary Incontinence Stop coping. Start living. What You should Know About Stress Urinary Incontinence	(Exhibit # unclear)
2012	Patient Brochure: Stress Urinary Incontinence Stop Coping. Start Living. What You Should Know about Stress Urinary Incontinence	ETH.MESH.09744858-63

VIII. Regulatory References
VIII. a. Code of Federal Regulations Title 21
21 CFR Part 7
21 CFR Part 201
21 CFR Part 202
21 CFR Part 801
21 CFR Part 803
21 CFR Part 806
21 CFR Part 807
21 CFR Part 810
21 CFR Part 814
21 CFR Part 820
21 CFR Part 860
VIII. b. Federal Food, Drug & Cosmetic Act and United States Code
15 U.S.C. 45
18 U.S.C. 1001
21 U.S.C. 321
21 U.S.C. 331
21 U.S.C. 351
21 U.S.C. 352
21 U.S.C. 360
FDCA 201
FDCA 502
FDCA 518
VIII. c. Other Regulatory Documents
Title
Device Advice – Class I/II Exemptions, US FDA/CDRH
Device Advice – General Controls for Medical Devices, US FDA/CDRH http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm
Device Advice – Labeling Requirements, US FDA/CDRH
60 Federal Register 63583
FDA Compliance Program Guidance Manual 7382.845, Attachment C
FDA Docket No. 2005N-0354
Content of a 510(k) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm142651.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=content%20of%20a%20510k&utm_content=1
FDA Device Advice: Device Regulation and Guidance. PMA Labeling http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050390.htm

VIII. c. Other Regulatory Documents (Continued)	
FDA Memorandum of Understanding Regarding Patient Labeling Review (Blue Book Memo #69-3).http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080258.htm	
Medical Devices: Labeling Requirements – Misbranding http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/GeneralDeviceLabelingRequirements/ucm052190.htm	
Medical Devices: Surgical Mesh http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm142636.htm	
Global Harmonization Task Force Website: http://www.ghtf.org/.	
Date	**Title**
June 30, 1986	Guidance on the CDRH Premarket Notification Review Program [K86-3]: 510(k) Memorandum #K86-3
April 1996	Medical Device Reporting: An Overview, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA
January 10, 1997	510(k) Memorandum #K97-1: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm
March 1997	Medical Device Reporting for Manufacturers, Prepared by Division of Small Manufacturers Assistance Office of Communication, Education, and Radiation Programs, FDA CDRH http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094529.htm
September 1997	Improving Patient Care by Reporting Problems with Medical Devices. A MedWatch Continuing Education Article. Uniformed Services University of the Health Sciences and FDA
March 20, 1998	The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance, US FDA/CDRH http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm
July 1, 1998	World Health Organization Calls First International Consultation on Incontinence – Leading Medical Experts Move to Reclassify Condition as a Disease and Set Treatment Guidelines. Press Release WHO/49
June 29, 1999	Global Harmonization Task Force (GHTF) FINAL DOCUMENT: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative
April 19, 2001	Center for Devices and Radiological Health, U.S. Food and Drug Administration. Guidance on Medical Device Patient Labeling
January 2003	GHTF FINAL DOCUMENT: Manufacturer's Trend Reporting of Adverse Events
July 2, 2003	Manual of Policies and Procedures MAPP 6020.10: NDAs: "Dear Health Care Professional" Letters, issued by CDER, FDA

VIII. c. Other Regulatory Documents (Continued)	
May 21, 2004	FDA Guidance for Industry and FDA Staff; FDA and Industry Actions on Premarket Notification 510(k)
March 2005	Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. U.S. FDA, CDER/CBER
January 18, 2006	Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events
November 30, 2006	GHTF FINAL DOCUMENT: Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices
July 19, 2007	Guidance for Industry and FDA Staff: Writing *Dear Doctor* Letters for Recalls of Implantable Cardioverter Defibrillators (ICDs), issued by CDRH, FDA.
August 19, 2008	AdvaMed (Advanced Medical Technology Association). The 510(k) Process: The Key to Effective Device Regulation http://www.elsevierbi.com/~/media/205258BC16894600AB9913836E9B72C3
December 11, 2008	Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision. http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089274.htm#4e.
April 17, 2009	Ulatowski: GHTF to Guide FDA Regulations, Guidances. The QMN Weekly Bulletin; Vol 1 No 16.
November 2010	Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of Important Safety Information, CDER/CBER, FDA.
November 16, 2010	Recalls, Corrections, and Removals (Devices): http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/RecallsCorrectionsAndRemovals/
March 8, 2011	Guidance for Industry and FDA Staff: Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence, CDRH, FDA.
July 2011	Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf
July 13, 2011	FDA Safety Communication: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm
July 13, 2011	FDA News Release: Surgical placement of mesh to repair pelvic organ prolapse poses risks http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm262752.htm
July 13, 2011	Transvaginal Placement of Surgical Mesh http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm079028.htm

VIII. c. Other Regulatory Documents (Continued)	
September 9, 2011	US Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee, Obstetrics and Gynecology Medical Devices Panel (Panel Members: Falcone T, Brill A, Davis A, Hillard PJ, Chappell R, et al.)
January 4, 2012	Medical Devices: Urogynecologic Surgical Mesh Implants http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/default.htm
May 23, 2013	522 Postmarket Surveillance Studies: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm?t_id=213&c_id=618
September 5, 2013	Medical Devices: Stress Urinary Incontinence (SUI) http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm
September 25, 2013	Medical Devices: How to Market Your Device http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm
VIII. d. Legal Cases	
United States v. Research Laboratories, Inc., 126 F.2d 42, 45 (9th Cir. 1942), *cert. denied*, 317 US 656 (1942).	

IX. Literature Articles	
Reference	
Debodinance P, et al. "TVT Secur: Prospective Study and Follow Up to 1 Year About 150 Patients." (Abstract only)	
de Tayrac R, et al. "A Prospective Randomized Study Comparing TVT and Transobturator Suburethral Tape (T.O.T.) for the Surgical Treatment of Stress Incontinence." (Abstract only)	
Haylen BT, et al. "An International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Terminology and Classification of the Complications Related Directly to the Insertion of Prostheses (Meshes, Implants, Tapes) & Grafts in Female Pelvic Floor Surgery."	
Gandhi S, et al. "Midurethral Tape Procedures: Are They All the Same?"	
Costa P, et al. "Trans-Obturator Tape (T.O.T.) For Female Stress Urinary Incontinence: Preliminary Results of a Prospective Multicenter Register." (Abstract only)	
Price N, et al. "Clinical audit of the use of tension-free vaginal tape as a surgical treatment for urinary stress incontinence, set against NICE guidelines."	
Hubka P, et al. "Possible Complications of the TVT-S Vaginal Tape in the H-Position." (Abstract only)	
Brubaker L, et al. "Surgery for Pelvic Organ Prolapse." Pp. 1275-1320	
Date	**Reference**
1984	Apple DJ, et al "Biocompatibility of implant materials: a review and scanning electron microscopic study." J Am Intraocul Implant Soc 1984;10(1):53-66. Abstract only.
1986	Altman AJ, et al. "The breakdown of polypropylene in the human eye: is it clinically significant?" Ann Ophthalmol 1986;18(5):182-185. Abstract only.
1986	Jongebloed WL, et al. "Degradation of polypropylene in the human eye: a SEM study." Doc Ophthalmol 1986;64(1):143-152. Abstract only.
1990	Petros PEP, et al. "An Integral Theory of Female Urinary Incontinence." Acta Obstet Gynecol Scand 1990;69 Suppl 153:7-31
1996	Julian TM. "The efficacy of Marlex mesh in the repair of severe, recurrent vaginal prolapse of the anterior midvaginal wall." Am J Obstet Gynecol 1996;175:1472-75
1997	Leach GE, et al "Female Stress Urinary Incontinence Clinical Guidelines Panel Summary Report on Surgical Management of Female Stress Urinary Incontinence" The Journal of Urology 1997;158(3):875-880
1997	Iglesia CB, et al. "The use of mesh in gynecological surgery." Int Urogynecol J 1997;8:105-115.
1998	Klinge U, et al. "Shrinking of polypropylene mesh in vivo: an experimental study in dogs." Eur J Surg 1998;164(12):965-969. Abstract only.
1999	Klinge U, et al "Foreign body reaction to meshes used for the repair of abdominal wall hernias." Eur J surg 1999;165(7):665-673. Abstract only.
2001	Nitti VW. "The Prevalence of Urinary Incontinence." Rev Urol. 2001;3(Suppl. 1):S2-S6

IX. Literature Articles (Continued)	
2001	Falconer C, et al "Influence of Different Sling Materials on Connective Tissue Metabolism in Stress Urinary Incontinent Women" Int Urogynecol J 2001;Suppl 2: S19-S23
2001	Jeffry L, et al. "Objective and subjective cure rates after tension-free vaginal tape for treatment of urinary incontinence." Urology 2001;58:702-706
2001	Nilsson CG, et al. "Long-term Results of the Tension-Free Vaginal Tape (TVT) Procedure for Surgical Treatment of Female Stress Urinary Incontinence." Int Urogynecol J 2001;Suppl 2:S5-S8
2001	Kuo HC. "Comparison of Video Urodynamic Results after the Pubovaginal Sling Procedure Using Rectus Fascia and Polypropylene Mesh for Stress Urinary Incontinence." The Journal of Urology 2001;165:163-168.
2001	Tamussino KF, et al. "Tension-free vaginal tape operation: results of the Austrian Registry." Am Coll Obstet Gynecol 2001;98(No. 5, Part 1):732-736
2001	Cervigni M, et al "The use of synthetics in the treatment of pelvic organ prolapse." Curr Opinion Urol 2001;1:429-435.
2002	Bodelsson G, et al. "Short term complications of the tension free vaginal tape operation for stress urinary incontinence in women." BJOG 2002;109:566-569
2002	Kuuva N, et al. "A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure." Acta Obstet Gynecol Scand 2002;81:72-77
2002	Ward K, Hilton P. "Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence." BMJ 2002;325:1-7
2002	Sweat SD, et al. "Polypropylene mesh tape for stress urinary incontinence: complications of urethral erosion and outlet obstruction." J Urol 2002;168:1440146
July 2002	Sweat SD, et al. "Polypropylene Mesh Tape for Stress Urinary Incontinence: Complications of Urethral Erosion and Outlet Obstruction." The Journal of Urology 2002;168:144-146
August 11, 2002	Robert Cohen, et al. "A surefire profit-maker could cost its maker dearly." *The Star Ledger*
2003	Karram MM, et al. "Complications and untoward effects of the tension-free vaginal tape procedure." Obstet Gynecol 2003;101:929-932
2003	De Leval. "Novel Surgical Technique for the Treatment of Female Stress Urinary Incontinence: Transobturator Vaginal Tape Inside-Out." European Urology 2003;44:724-730
2003	Cody J, et al. "Systemic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence." Health Technology Assessment 2003;7(21)
2003	Rosch R, et al. "Mesh implants in hernia repair. Inflammatory cell response in a rat model." Eur J Surg 2003;35(3):161-166. Abstract only.
2003	Dietz HP, et al. "Mechanical properties of urogynecologic implant materials." Int Urogynecol J 2003;14:239-243
May 2003	Muir TW, et al. "The Relationship of Tension-Free Vaginal Tape Insertion and the Vascular Anatomy." Obstetrics & Gynecology 2003;101(5):933-936. Doi: 10.1016/S0029-7844(03)00011-5

IX. Literature Articles (Continued)	
2004	Turner DA, et al. "The cost of clinically significant urinary storage symptoms for community dwelling adults in the UK." BJU Int 2004;93:1246-1252
2004	Levin I, et al. "Surgical Complications and Medium-Term Outcome Results of Tension-Free Vaginal Tape: A Prospective Study of 313 Consecutive Patients." Neurology and Urodynamics 2004;23:7-9
2004	Ansquer Y, et al. "The suburethral sling for female stress urinary incontinence: a retropubic or obturator approach?" J Am Assoc Gynecol Laparoscopists 2004;11:353-358
2004	Whiteside JL, et al. "Anatomy of the obturator region: relations to a trans-obturator sling." Int Urogynecol J 2004;15:223-226. Doi: 10.1007/s00192-004-01143-y
2004	Ward KL, et al. "A prospective multicenter randomised trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: Two-year follow-up." Am J Obstet Gynecol 2004;190:324-331
2004	Abouassaly R, et al. "Complications of tension-free vaginal tape surgery: a multi-institutional review." BJU Int 2004;94:110-113
2004	Flock F, et al. "Hemorrhagic complications associated with tension-free vaginal tape procedure." Obstet Gynecol 2004:104:989-994
2004	Delorme E, et al. "Transobturator Tape (Uratape): A New Minimally-Invasive Procedure to Treat Female Urinary Incontinence." European Urology 2004;45:203-207
2004	Samore MH et al. "Surveillance of medical device-related hazards and adverse events in hospitalized patients." *JAMA* 2004;291:325-334.
2004	Paraiso MF, et al. "Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial." Obstet Gynecol 2004;104:1249-1258
2004	Bhargava S, et al. "Rising awareness of the complications of synthetic slings." Curr Opin Urol 2004;14:317-321
2004	Wang AC, et al. "A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: A prospective case-controlled pilot study." American Journal of Obstetrics and Gynecology 2004;191:1868-74 (ETH.MESH.00523348)
November 2004	Flock F, et al. "Hemorrhagic Complications Associated With Tension-free Vaginal Tape Procedure." Obstet Gynecol 2004;104:989-94
2005	Lim YN, et al. "Suburethral slingplasty evaluation study in North Queensland Australia: The SUSPEND trial." Australian and New Zealand Journal of Obstetrics and Gynaecology 2005;45:52-59
2005	Tseng LH, et al. "Randomized comparison of the suprapubic arc sling procedure vs tension-free vaginal taping for stress incontinent women." Int Urogynecol J 2005;16:230-235. Doi: 10.1007/s00192-004-1248-3
2005	Balkwill F, et al. "Smoldering and polarized inflammation in the initiation and promotion of malignant disease." Cancer Cell 2005;7:211-217
2005	Atherton MJ, et al. "The tension-free vaginal tape reviewed: an evidence-based review from inception to current status." BJOG 2005;112:534-546

IX. Literature Articles (Continued)	
2005	Bonnet P, et al. "Transobturator vaginal tape inside out for the surgical treatment of female stress urinary incontinence: anatomical considerations." The Journal of Urology 2005;173:1223-1228. Doi: 10.1097/01.ju.0000148364.13525.7b
2005	Simsiman AJ, et al. "Suburethral sling materials: Best outcome with autologous tissue." American Journal of Obstetrics and Gynecology 2005;193:2112-16
2005	Morley R, et al. "Minimally invasive surgical techniques for stress incontinence surgery." Best Practice & Research Clinical Obstetrics and Gynaecology 2005;19(6):925-940. Doi: 10.1016/j.bpobgyn.2005.08.014
2005	Fischer A, et al. "Comparison of Retropubic and Outside-In Transobturator Sling Systems for the Cure of Female Genuine Stress Urinary Incontinence." European Urology 2005;48:799-804
2005	Giri SK, et al. "A magnetic resonance imaging-based study of retropubic haematoma after sling procedures: preliminary findings." BJU 2005:1067-71
2005	Andonian S, et al. "Randomized Clinical Trial Comparing Suprapubic Arch Sling (SPARC) and Tension-Free Vaginal Tape (TVT): One-Year Results." European Urology 2005;47:537-541
2005.	Bright RA and Shen J. Use of a free, publicly-accessible data source to estimate hospitalizations related to adverse medical device events. Draft manuscript,
2006	Liapis A, et al. "Tension-Free Vaginal Tape versus Tension-Free Vaginal Tape Obturator in Women with Stress Urinary Incontinence." Gynecol Obstet Invest 2006;62:160-164. Doi: 10.1159/000093320
2006	Howden NS, et al. "Comparison of autologous rectus fascia and cadaveric fascia in pubovaginal sling continence outcomes." American Journal of Obstetrics and Gynecology 2006;194:1444-49
2006	David-Montefiore E, et al. "Peri-Operative Complications and Pain After the Suburethral Sling Procedure for Urinary Stress Incontinence: A French Prospective Randomised Multicentre Study Comparing the Retropubic and Transobturator Routes." European Urology 2006;49:133-138
2006	Lord HE, et al. "A randomized controlled equivalence trial of short-term complications and efficacy of tension-free vaginal tape and suprapubic urethral support sling for treating stress incontinence." BJU 2006;98:367-376
2006	Deprest J et al. "The biology behind fascial defects and the use of implants in pelvic organ prolapse repair." Int Urogynecol J 2006;17:S16-S25.
March 2006	Morey AF, et al. "Transobturator Versus Transabdominal Mid Urethral Slings: A Multi-Institutional Comparison of Obstructive Voiding Complications." The Journal of Urology 2006;175:1014-1017
April 13, 2006	Brubaker L, et al. "Abdominal Sacrocolpopexy with Burch Colposuspension to Reduce Urinary Stress Incontinence." N Engl J Med 2006;354:1557-66
2007	Albo ME, et al. "Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence." The New England Journal of Medicine 2007;356:2143-55
2007	Deng DY, et al. "Presentation and management of major complications of midurethral slings: Are complications under-reported?" Neurourology Urodynamics 2007:26:46-52

IX. Literature Articles (Continued)	
2007	Latthe PM, et al. "Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications." BJOG 2007;114:522-531
2007	Hinoul P, et al. "Anatomical variability in the trajectory of the inside-out transobturator vaginal tape technique (TVT-O)." Int Urogynecol J 2007;18:1201-1206. Doi: 10.1007/s00192-007-0303-2
2007	Meschia M, et al. "Peri-operative morbidity and early results of a randomised trial comparing TVT and TVT-O." Int Urogynecol J 2007;18:1257-1261. Doi: 10.1007/s00192-007-0334-8
2007	Zullo MA, et al. "One-Year Follow-up of Tension-free Vaginal Tape (TVT) and Trans-obturator Suburethral Tape from Inside to Outside (TVT-O) for Surgical Treatment of Female Stress Urinary Incontinence: A Prospective Randomised Trial." European Urology 2007;51:1376-1384
2007	Spinosa JP, et al. "Transobturator surgery for female stress incontinence: a comparative anatomical study of outside-in vs inside-out techniques." BJU International 2007;100:1097-1102
2007	Porena M, et al. "Tension-Free Vaginal Tape versus Transobturator Tape as Surgery for Stress Urinary Incontinence: Results of a Multicentre Randomised Trial." European Urology 2007;52:1481-1491
2007	Gilberti C, et al. "Transobturator Tape for Treatment of Female Stress Urinary Incontinence: Objective and Subjective Results After a Mean Follow-up of Two Years." Urology 2007;69:703-707
2007	Juang CM, et al. "Efficacy Analysis of Trans-obturator Tension-free Vaginal Tape (TVT-O) Plus Modified Ingelman-Sundberg Procedure versus TVT-O Alone in the Treatment of Mixed Urinary Incontinence: A Randomized Study." European Urology 2007;51:1671-1679
2007	Drazen JM et al. "Current adverse event reporting systems. Adverse Drug Event Reporting: The Roles of Consumers and Health-Care Professionals: Workshop Summary, Forum on Drug Discovery, Development, and Translation." *National Academy of Sciences*
2007	Costello CR, et al. "Materials characterization of explanted polypropylene hernia meshes." J Biomed Mater Res Part B:Appl Biomater 2007;83B: 44–49.
2007	Gold RS, et al. "Bladder Perforation During Tension-Free Vaginal Tape Surgery: Does It Matter?" J Reprod Med 2007;52:616-618
2007	Juma S, et al. "Transobturator Tape (TOT): Two Years Follow-Up." Neurourol. Urodynam 2007;26:37-41
2007	Debodinance P. "Trans-obturator urethral sling for the surgical correction of female stress urinary incontinence: Outside-in (Monarc) versus inside-out (TVT-O) Are the two ways reassuring?" European Journal of Obstetrics & Gynecology and Reproductive Biology 2007;133:232-238
January 2007	Laurikainen E, et al. "Retropubic Compared with Transobturator Tape Placement in Treatment of Urinary Incontinence: A Randomized Controlled Trial." Obstet Gynecol 2007;109:4-11

IX. Literature Articles (Continued)	
March 2007	Anger JT, et al. "Complications of Sling Surgery Among Female Medicare Beneficiaries." Obstetrics & Gynecology 2007;109(3):707-14
July 2007	Sung VW, et al. "Comparison of retropubic vs transobturator approach to midurethral slings: a systematic review and meta-analysis." American Juournal of Obstetrics & Gynecology 2007:3-11
2008	Schierlitz L, et al. "Effectiveness of Tension-Free Vaginal Tape Compared With Transobturator Tape in Women with Stress Urinary Incontinence and Intrinsic Sphincter Deficiency." Obstet Gynecol 2008;112:1253-61
2008	Barber MD, et al. "Transobturator Tape Compared With Tension-Free Vaginal Tape for the Treatment of Stress Urinary Incontinence: A Randomized Controlled Trial." Obstet Gynecol 2008;111:611-21
2008	Barry C, et al. "A multi-centre, randomised clinical control trial comparing the retropubic (RP) approach versus the transobturator approach (TO) for tension-free, suburethral sling treatment of urodynamic stress incontinence: the TORP study." Int Urogynecol J 2008;19:171-178
2008	Waltregny D, et al. "TVT-O for the Treatment of Female Stress Urinary Incontinence: Results of a Prospective Study after a 3-Year Minimum Follow-Up." European Urology 2008;53:401-410
2008	Ward KL, et al. "Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up." BJOG 2008;115:226-233
2008	Ridgeway BM, et al. "Variation of the obturator foramen and pubic arch of the female bony pelvis." Am J Obstet Gynecol 2008;198:546.e1-546.e4
2008	Barber MD, et al. "Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence." Obstet Gynecol 2008;111:611-621
2008	Rinne K, et al. "A randomized trial comparing TVT with TVT-O: 12-month results." Int Urogynecol J 2008;19:1049-1054
2008	Moalli PA, et al. "Tensile properties of five commonly used mid-urethral slings relative to the TVT." Int Urogynecol J 2008;19:655-663
2008	Liapis A, et al. "Monarc vs TVT-O for the treatment of primary stress incontinence: a randomized study." Int Urogynecol J 2008;19:185-190
2008	Neuman M. "Perioperative Complications and Early Follow-up with 100 TVT-SECUR Procedures." Journal of Minimally Invasive Gynecology 2008;15:480-484
2008	But I, et al. "Complications and short-term results of two different transobturator techniques for surgical treatment of women with urinary incontinence: a randomized study." Int Urogynecol J 2008;19:857-861
2008	Jelovsek JE, et al. "Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow-up." BJOG 2008;115:219-225
2008	Abstracts from Journal of Minimally Invasive Gynecology 2008;15:S28
2008	Nilsson CG, et al. "Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence." Int Urogynecol J 2008;19:1043-1047
2008	Deng M, et al. "A study on in vitro degradation behavior of a poly(glycolide-co-L-lactide) monofilament." Acta Biomaterialia 2008;4:1382-1391

IX. Literature Articles (Continued)	
2008	Twiss C, et al. "Complications of synthetic mid-urethral slings." Issues in Incontinence. Laborie.com, Spring/Summer 2008
2008	Nazemi TM, et al. "Minimum 24-Month Followup of the Sling for the Treatment of Stress Urinary Incontinence." The Journal of Urology 2008;179:596-599. Doi: 10.1016/j.juro.2007.09.069
2008	Noblett KL, et al. "Lynx midurethral sling system: a 1-year prospective study on efficacy and safety." Int Urogynecol J 2008. Doi: 10.1007/s00192-008-0624-9
2008	Gebhart JB, et al. "Three-year outcomes of Uretex Urethral Support System for treatment of stress urinary incontinence." Int Urogynecol J 2008;19:1075-1079. Doi: 10.1007/s00192-008-0578-y
2008	Araco F, et al. "TVT-O vs TVT: a randomized trial in patients with different degrees of urinary stress incontinence." Int Urogynecol J 2008;19:917-926. Doi: 10.1007/s00192-007-0554-y
July 2008	Brubaker L, et al. "Two-Year Outcomes After Sacrocolpopexy With and Without Burch to Prevent Stress Urinary Incontinence." Obstet Gynecol 2008;112(1):49-55. Doi: 10.1097/AOG.0b013e3181778d2a
2009	Oliphant SS, et al. "Trends in stress urinary incontinence inpatient procedures in the United States, 1979-2004." Am J Obstet Gynecol 2009;200:521e1-521-e6
2009	Elmer C, et al. "Histological inflammatory responses to transvaginal polypropylene mesh for pelvic reconstructive surgery." U Urol 2009;181(3):1189-1195. Abstract only.
2009	Rardin CR, et al. "Case Report: Recurrent Thigh Abscess with Necrotizing Fasciitis from a Retained Transobturator Sling Segment." Journal of Minimally Invasive Gynecology 2009;16:84-87
2009	Amaro, JL, et al. "Clinical and quality-of-life outcomes after autologous fascial sling and tension-free vaginal tape: A prospective randomized trial." Int Braz J Urol 2009:35:60-67
2009	Atis G, et al. "Tissue Reaction of the Rat Urinary Bladder to Synthetic Mesh Materials." The Scientific World Journal 2009;9:1046-1051. Doi: 10.1100/tsw.2009.120
October 2008	Oliveira R, et al. "Short-term assessment of a tension-free vaginal tape for treating female stress urinary incontinence." BJU 2009:225-228
2009	Hazewinkel MH, et al. "Persistent groin pain following a trans-obturator sling procedure for stress urinary incontinence: a diagnostic and therapeutic challenge." Int Urogynecol J 2009;20:363-365. Doi: 10.1007/s00192-008-0714-8
August 2009	Anger JT, et al. "Trends in the Surgical Management of Stress Urinary Incontinence among Female Medicare Beneficiaries." Urology 2009;74(2):283-287. Doi: 10.1016/j.urology.2009.02.011
2010	Krofta L, et al. "TVT-S for surgical treatment of stress urinary incontinence: prospective trial, 1-year follow-up." Int Urogynecol J 2010;21:779-785. Doi: 10.1007/s00192-010-1128-y
2010	Nieminen K, et al. "Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up." Am J Obstet gynecol 2010;203:235.e1-8

IX. Literature Articles (Continued)	
2010	Abdel-fattah M, et al. "Randomised prospective single-blinded study comparing 'inside-out' versus 'ouside-in' transobturator tapes in the management of urodynamic stress incontinence: 1-year outcomes from the E-TOT study." BJOG 2010:870-78
2010	Tommaselli GA, et al. "Efficacy and safety of TVT-O and TVT-Secur in the treatment of female stress urinary incontinence: 1-year follow-up." Int Urogynecol J 2010;21:1211-1217
2010	Kim JJ, et al. "Randomized Comparative Study of the U- and H-Type Approaches of the TVT-Secur Procedure for the Treatment of Female Stress Urinary Incontinence: One-Year Follow-Up." Korean J Urol 2010;51:250-256
2010	"One year results of a prospective randomized trial comparing the original inside-out transobturator (TVT-O) procedure and a modified version using a shortened tape and reduced dissection for the treatment of female stress urinary incontinence." (Abstract Only) ICS-IUGA 2010 Abstract Form
2010	Richter HE, et al. "Retropubic versus transobturator midurethral slings for stress incontinence." NEJM 2010;362:2066-2076
2010	Mathewson NW. Complaint Handling and Medical Device Reporting. In *Medical Device Regulation & Compliance*. Eds. Terman SD and O'Flaherty NF. FDLI 2010.
February 2010	Feiner B, et al. "Vaginal Mesh Contraction: Definition, Clinical Presentation, and Management." Obstet Gynecol 2010;115:325-30
August 2010	Iglesia CB, et al. "Vaginal Mesh for Prolapse: A Randomized Controlled Trial." Obstet Gynecol 2010;116:293-303
2011	de Leval J, et al. "The original versus a modified inside-out transobturator procedure: 1-year results of a prospective randomized trial." Int Urogynecol J 2011;22:145-156
2011	Hinoul, et al. "An anatomic comparison of the original versus a modified inside-out transobturator procedure." Int Urogynecol J 2011;22:997-1004
2011	Ying-he C, et al. "Efficacy and postoperative complication of tension-free vaginal tape-Secur for female stress urinary incontinence." Chin Med J 2011;124(9):1296-1299
2011	Brubaker L, et al. "Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study." Am J Obstet Gynecol 2011;205:498e1-e6
2011	Hamer MA, et al. "Short term results of a prospective randomized evaluator blinded multicenter study comparing TVT and TVT-Secur." Int J Urogynecol 2011;22:781-787
2011	Oliveira R, et al. "Exploratory Study Assessing Efficacy and Complications of TVT-O, TVT-Secur, and Mini-Arc: Results at 12-Month Follow-Up." European Urology 2011;59:940-944
2011	Abdel-Fattah M, et al. "Single-Incision Mini-Slings Versus Standard Midurethral Slings in Surgical Management of Female Stress Urinary Incontinence: A Meta-Analysis of Effectiveness and Complications." European Urology 2011;60:468-480
2011	Wu JM, et al. "Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050." Am J Obstet Gynecol 2011;205:230e1-230e5

IX. Literature Articles (Continued)	
2011	Blaivas JG, et al. "Pubovaginal Fascial Sling for the Treatment of all Types of Stress Urinary Incontinence: Surgical Technique and Long-term Outcome." Urol Clin N Am 2011;38:7-15
2011	Chen X, et al. "A modified inexpensive transobturator vaginal tape inside-out procedure versus tension-free vaginal tape for the treatment of SUI: a prospective comparative study." Arch Gynecol Obstet 2011;284:1461-1466
2011	Ogah J, et al. "Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane Review." Neurol Urodynam 2011;30:284-291
2011	Walsh CA. "TVT-Secur mini-sling for stress urinary incontinence: a review of outcomes at 12 months." BJU International 2011;108:652-657. Doi: 10.1111/j.1464-410X.2011.10333.x
2011	Abed H, et al. "Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review." Int Urogynecol J 2011;22:789-798. Doi: 10.1007/s00192-011-1384-5
March 2011	Jaburek L, et al. "Risk of Haemorrhagic Complications of Retropubic Surgery in Females: Anatomic Remarks." Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2011;155(1):75-78. Doi: 10.5507/bp.2011.014
April 2011	Teo R, et al. "Randomized Trial of Tension-Free Vaginal Tape and Tension-Free Vaginal Tape-Obturator for Urodynamic Stress Incontinence in Women." The Journal of Urology 2011;185:1350-1355. Doi: 10.1016/j.juro.2010.11.064
July 13, 2011	FDA Safety Communication: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse
October 27, 2011	Alex Nussbaum, et al. "J&J Mesh Approved by FDA Based on Recalled Device." Bloomberg http://mobile.bloomberg.com/news/2011-10-20/j-j-vaginal-mesh-approved-by-fda-based-on-older-recalled-device
December 2011	Tincello DG, et al. "The TVT Worldwide Observational Registry for Long-Term Data: Safety and Efficacy of Suburethral Sling Insertion Approaches for Stress Urinary Incontinence in Women." The Journal of Urology 2011;186:2310-2315
2012	Kwon SY, et al. "Inflammatory myofibroblastic tumor of the urinary tract following a TVT." Female Pelvic Med Reconstruct Surg 2012;18:249-251
2012	Albo ME, et al. "Treatment success of retropubic and transobturator mid urethral slings at 24 months." J Urol 2012;188:2281-2287
2012	Funk MJ, et al. "Long-term outcomes after stress urinary incontinence surgery." Obstet Gynecol 2012;120:83-90
2012	Serati M, et al. "Tension-free vaginal tape for the treatment for urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up." Eur Urology 2012;61:939-946
2012	Kwon SY, et al. "Inflammatory myofibroblastic tumor of the urinary tract following a TVT." Female Pelvic Med Reconstruct Surg 2012;18:249-251
2012	Barber MD, et al. "Single-Incision Mini-Sling Compared With Tension-Free Vaginal Tape for the Treatment of Stress Urinary Incontinence: A Randomized Controlled Trial." Obstet Gynecol 2012;119:328-37. Doi: 10.1097/AOG.0b013e318242a849

IX. Literature Articles (Continued)	
2012	Lapitan MCM, et al. "Open retropubic colposuspension for urinary incontinence in women (Review)." The Cochrane Collaboration 2012. Published by JohnWiley & Sons, Ltd.
2012	Hota LS, et al. "TVT-Secur (Hammock) Versus TVT-Obturator: A Randomized Trial of Suburethral Sling Operative Procedures." Female Pelvic Med Reconstr Surg 2012;18:41-45
2012	Ortega-Castillo V, et al. "Surgical complications with synthetic materials, Urinary Incontinence." Alhasso A, ed. InTech 2012. http://www.intechopen.com/books/urinary-incontinence/complications-of-genital-prolapse-and-urinaryincontinence-surgery
January 2012	Brill AI. "The hoopla over mesh: what it means for practice." OB GYN News
July 2012	Jonsson Funk M, et al. "Long-Term Outcomes After Stress Urinary Incontinence Surgery." Obstet Gynecol 2012;120(1):83-90. Doi: 10.1097/AOG.0b013e318258fbde.
September 2012	Sternschuss G, et al. "Post-implantation alterations of polypropylene in the human." J Urol 2012;188(1):27-32. Doi: 10.1016/j.juro.2012.02.2559. (Abstract only)
2013	Birolini C, et al. "Mesh cancer: long-term mesh wall infection leading to squamous-cell carcinoma of the abdominal wall." Hernia, published online 19 April 2013
2013	Firoozi, et al. "Pure transvaginal excision of mesh erosion involving the bladder." Int Urogynecol J 2013. DOI 10.1007/s00192-013-2082-2
2013	Tirlapur SA, et al. "Nerve stimulation for chronic pelvic pain and bladder pain syndrome: a systematic review." (Abstract only). Doi: 10.1111/aogs.12184
2013	Klosterhalfen B, et al. "Retrieval study at 623 human mesh explants made of polypropylene – impact of mesh class and indication for mesh removal on tissue reaction." J Biomed Mater Res Part B 2013:1-7
2013	Basu M, et al. "Three-year results from a randomised trial of a retropubic mid-urethral sling versus the Miniarc single incision sling for stress urinary incontinence." Int Urogynecol J 2013
2013	Rogowski A, et al. "Mesh retraction correlates with vaginal pain and overactive bladder symptoms after anterior vaginal mesh repair." Int Urogynecol J 2013. Doi: 10.1007/s00192-013-2131-x
January 28, 2013	Nilsson CG, et al. "Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence." Int Urogynecol J 2013(ETH.MESH.08299913-17)
May 15, 2013	Iglesia CB. "Pelvic Organ Prolapse Surgery: Long-term Outcomes and Implications for Shared Decision Making." JAMA 2013;309:19

Peggy Pence, PhD, RAC, FRAPS
Expert Witness Report
Ethicon, Inc. Pelvic Repair System,
Products Liability Litigation

Appendix C: Literature Review

October 14, 2013

Dr. Peggy Pence PhD, RAC, RAPS Fellow
Expert Witness Report – Appendix C
Literature Review

ULMSTEN STUDIES – DEVELOPER OF TVT TECHNIQUE

Ulmsten U, Henriksson L, Johnson P, Varhos G. An ambulatory surgical procedure under local anesthetic for treatment of female urinary incontinence. Int Urogynecol J 1996:7:81-86.

This article describes a surgical approach to correcting stress urinary incontinence (SUI) by permanent implantation of a polypropylene sling (prolene) intravaginally. This procedure later became known as TVT.

Seventy-five consecutive patients with SUI and no prior surgeries were enrolled in this single-center study conducted at Uppsala University, Sweden. The mean age was 52 years (range: 36-81) and mean parity 1.5 (range: 0-3). Preoperative assessments included full urodynamic investigation with urethral pressure profile measurements, urethrocystometry with stress provocation, urine flow measurement, 24-hour pad test and a modified life quality assessment. All patients were on estrogen therapy. Postoperative evaluations were done at 2, 6, 12, and 24 months.

A Prolene gauze sling 40 cm long and 10 cm wide, covered by a plastic sheath, was inserted via a metal handle to which metal or plastic needles were attached. One 2-cm or two 1-cm transverse incisions were made close to the superior rim of the pubic bone. Another incision ≤ 1.5 cm was made in the midline of the suburethral vaginal wall, starting approximately 0.5 cm from the outer urethral meatus. Laterally from this incision a blunt dissection 0.5-1.0 cm long was made with scissors to each side of the urethra. Using the handle with needles attached, the tip of the needle was inserted into the prepared paraurethral incision on the right side of the urethra. The urogenital diaphragm was perforated, and the tip of the needle was brought up to the abdominal incision by "shaving" the back of the pubic bone. As soon as the needle tip had reached the abdominal skin incision, the proximal end of the needle was disconnected from the handle, and the sling covered by the plastic sheath was brought into position by pulling the needle upwards with the sling attached. The procedure was then repeated on the left side. When the sling had been placed in a U shape around the mid-urethra, the plastic sheath was withdrawn. The sling was placed loosely, and the abdominal ends were not fixed but cut with scissors below the skin surface. Finally, the skin and vaginal incisions were sutured.

No patient experienced intra- or postoperative bleeding >300 mL, and no bladder perforations occurred. All patients were able to be released by the morning of the day after surgery. At follow-up examinations, 63 of 75 patients (84%) reported no leakage, which was confirmed by repeated stress tests in the continence clinic. In six patients, occasional leakage occurred in severe stress situations, such as vigorous coughing during severe cold. These patients considered themselves cured and did not wear pads. No leakage was observed during stress tests in the continence clinic. A preliminary analysis of the quality of life data showed significant positive change for all 69 patients who were either cured or substantially improved. The remaining six patients showed no objective or

subjective improvement. Failure of the procedure was evident within two months after surgery, and no further failures occurred beyond that time.

Five patients showed signs of postoperative urinary infection within 14 days after surgery. No specific bacteria were found, and all were treated successfully with conventional antibiotics. There were no signs of increased urinary infections during the remainder of follow-up. Five patients had immediate postoperative voiding problems necessitating an indwelling catheter over the first postoperative night. Otherwise, there were no cases of postoperative urinary retention and no long-term catheter treatment. There were no signs of defect healing or rejection of the sling in any of the patients.

All of the surgeons involved in this study were experienced in vaginal surgery. However, the authors noted that preliminary findings from a large multicenter study (see Ulmsten et al. 1998) involving less experienced surgeons reported similar results. They concluded that this is a promising new technique but stated that long-term results in a larger series of prospective studies must be obtained before the ultimate place of a new surgical method can be established.

Ulmsten U, Falconer C, Johnson P, Jomaa M, Lanner L, Nilsson CG, et al. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. Int Urogynecol J 1998;9:210-213.

This was a prospective, multicenter study of the TVT procedure described in the Ulmsten et al. 1996 article. The purpose was to determine the safety and effectiveness of the procedure as treatment of SUI when carried out by "ordinary" gynecologic units. (In the 1996 article, all of the participating surgeons were experienced in vaginal surgery, and it was considered that this might have influenced the outcomes as "too positive.") Each of six centers in Sweden provided two to three patients for learning the procedure under the direction of an experienced surgeon from Uppsala University. Surgeons from each center then performed the operation on approximately 20 consecutive patients. Pre- and postoperative assessments included stress provocation tests, pad tests, urodynamic investigations, and quality of life assessments. Follow-up assessments were done at 2, 6 and 12 months post-surgery.

A total of 131 patients were evaluated in this study. None had had prior surgery for SUI, and none had evidence of vaginal prolapse. The mean age was 53 years (range: 35-88) and mean parity 2 (range: 0-5). All patients were followed for 12 months. The cure rate (defined as <10 g/24-hr leakage on pad testing as well as no leakage with repeated coughs, and a ≥90% improvement on the quality of life [VAS]) was 92% (119/131). Another nine patients (7%) were judged significantly improved (no leakage at stress test, significantly reduced leakage on the 24-hour pad test, and >75% improvement on VAS). The remaining three patients showed improvement that did not meet the criteria of significantly improved, and these were therefore classified as failures.

One patient experienced a bladder perforation, and one experienced wound infection in the vaginal wall incision. Both patients were treated successfully, and both became

continent. In three patients, short-term (≤ 3 days) urinary retention occurred, requiring an indwelling catheter for three days. A fourth patient had voiding problems for 14 days, requiring adjustment of the tape through the vaginal incision, after which she voided normally. No tape rejection occurred (Prolene, Ethicon).

The authors concluded that this technique can be successfully performed by surgeons without specialized training. They attribute this to the fact that the technique is fairly simple and well-standardized and to the specific instruments designed for this surgery. They emphasize that the tape must be placed loosely under the mid-urethra, with no elevation allowed, to avoid postoperative urine retention.

Ulsten U, Johson P, Rezapour M. A three-year follow-up of tension free vaginal tape for surgical treatment of female stress urinary incontinence. Br J Obstet Gynaecol 1999;106:345-350.

This study followed patients with SUI for three years after having a TVT procedure according to the method reported by Ulmsten et al. 1996. Patients with urge incontinence or vaginal prolapse were excluded. Fifty women were enrolled, all of whom had had symptoms for more than three years. The mean age was 57 years; 42 women were multiparous and eight were nulliparous. All postmenopausal women were taking systemic or local estrogen therapy. Post-surgical follow-ups were performed after 2 to 6, 12, 24 and 36 months. Evaluations included stress provocation tests, 24-48-hour pad test, quality of life, urodynamic evaluation with urethrocystometry and urethral profile measurement, and recording of complications. Three experienced urogynecologic surgeons performed the operations. Cure was defined as <10 g/24-hr leakage on pad testing as well as no leakage with stress provocation (repeated coughs), a ≥90% satisfaction in the quality of life VAS, no urinary retention or residual urine volume > 100 mL. Significant improvement was defined as no incontinence on stress provocation, > 75% satisfaction via VAS, and no postoperative urinary retention or urge incontinence.

All but one patient received only local anesthesia. A very obese patient was operated on under spinal anesthesia. Eight-six (86) percent of patients (43/50) were cured, 12% (6/50) were significantly improved, and one met neither of these criteria, and thus was classified as a failure. No severe bleeding, urinary retention, recurrent urinary infection, defective healing or tape rejection occurred intra- or postoperatively. Two patients required repeated catheterization for two and three days. Three patients required an indwelling catheter for 7 to 12 days. The only change from pre- to postoperative urodynamic recordings was that urethral closure pressures at stress went from negative to positive in cured patients. There were no changes in postoperative outcomes over the three-year follow-up period.

The authors conclude that TVT is a safe and effective surgical technique for the treatment of SUI, with durable outcomes over at least three years. They note that the technique must ultimately be validated in prospective, randomized controlled clinical trials.

Nilsson CG, Kuuva N, Falconer C, Rezapour M, Ulmsten U. Long-term results of the tension-free vaginal tape (TVT) procedure for surgical treatment of female stress urinary incontinence. Int Urogynecol J 2001;Suppl 2:S5-S8.

This is a 5-year follow-up report of 90 patients with SUI who received slings according to the Ulmsten method (retropubic placement, Ulmsten 1998). Inclusion criteria were a history of SUI, positive cough stress test, and urodynamically proven stress incontinence. Patients with prior surgery for incontinence or a need for concomitant surgery, detrusor activity, or a maximal urethral closure pressure < 20 cm were excluded. Objective evaluations after the surgery included a cough stress test, a 24-hr pad test, residual urine volume measurements and a gynecological exam to detect tape erosion or other adverse tissue effects. Subjective outcomes were assessed with the following validated questionnaires: Incontinence Impact Questionnaire-short form (IIQ-7), Urogenital Distress Inventory (UDI-6), Urinary Incontinence Severity Score (UISS), and the Detrusor Instability Score (DIS). The Patients Global Impression (PGI) of the patients' continence status was assessed by asking the patients if they felt that they were cured or improved of their incontinence or if they felt the treatment had failed. Quality of life was assessed using a visual analog scale where 0 represented no urinary problems and 100 represented unbearable urinary complaints.

At the 5-year follow-up, cure was defined as a negative stress test, negative 24-hr pad test, and ≥90% improvement in QOL. Improvement was defined as a ≥75% improvement in QOL, and a >50% reduction in urine loss by the 24-hr pad test. At the 11-year follow-up, objective cure was defined as a negative stress test, and a negative 24-hr pad test. Subjective cure was defined by the patient's PGI of her continence status.

Eighty-five of the original 90 patients were evaluated at the clinic after five years. The remaining five patients were interviewed by phone or at the nursing home where they then resided. Of the 85 patients who were followed according to the protocol, 84.7% (72/85) were cured, 10.6% (9/85) were improved, and 4.7% (4/85) were considered failures. The five patients interviewed reported one cure, two improved, and two failures. Both of the latter reported being symptom-free until intercurrent diseases occurred. Three patients had a retropubic hematoma, one patient had a bladder perforation, and three patients had intraoperative bleeding of >200 mL. None of these complications required surgical intervention. [see Nilsson, 2004 and 2008 for 7- and 11-year follow-ups]

Nilsson CG, Falconer C, Rezapour M. Seven-year follow-up of the tension-free vaginal tape procedure for treatment of urinary incontinence. Obstet Gynecol 2004;104:1259-1262.

This is a 7-year follow-up report of patients who received TVT slings. Preliminary results were reported by Ulmsten et al., 1998, and a 5-year follow-up was reported by Nilsson et al., 2001. Of the original 90 patients enrolled in the trial, 64 were able to be objectively and subjectively evaluated after 7 years and an additional 16 provided subjective assessments via questionnaire. Objective evaluations included a cough stress test, 24-hour pad test, and a 2-day voiding diary. The mean follow-up was 91.1 months (range 78-100),

or 7.6 years. Of the 64 women who were fully evaluated, 54 (84.4%) had a negative pad test, 7 (10.9%) had a positive pad test (range 10 - 132g per 24 hours) ,and 3 women refused to perform the pad test, claiming they were completely dry. The stress test was not possible to perform in the standardized way in 3 women, and the remaining 61 (95.3%) women had a negative stress test. The criteria for objective cure were met by 81.3% of the clinically evaluated women. The subjective cure rate for all 80 patients was also 81.3%.

Eighteen (22.5%) of the evaluated 80 women had symptoms of urge. Asymptomatic pelvic organ prolapse, grade I-ll and not requiring surgical intervention, was seen in 5 (7.8%) of the 64 women seen at the clinics. Recurrent urinary tract infections were reported by 6 (7.5%) of 80 women interviewed. Five (6.3%) of 80 reported de novo urge symptoms. None of the women complained of voiding difficulties, and no sign of tape material rejection could be seen or was reported.

Compared to the 5-year follow-up data, 88% of women felt that their continence status was unchanged, 5% felt that it had improved, and 8% felt that it had worsened. The authors noted that changes in overall health status and lifestyle may have accounted for some of the negative perceptions. Overall, the authors conclude that the TVT procedure is effective over a period of 7 years.

Nilsson CG, Palva K, Rezapour M, Falconer C. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J 2008;19:1043-1047.

This is an 11-year follow-up report of patients who received TVT slings in the Ulmsten 1998 study. Preliminary results were reported by Ulmsten et al., 1998, and 5- and 7-year follow-ups were reported by Nilsson et al., 2001 and 2004. Of the 90 original patients, 69 were able to be evaluated after 11 years, although not all patients contributed data for each endpoint. Fifty-three (53) women were seen at clinics and sixteen (16) were contacted outside the clinics. At this time point, objective cure was defined as a negative stress test and a negative 24-hr pad test. Subjective cure was defined by a patient's global impression of her continence status. Fifty-five of 61 women had both a negative stress test and a negative pad test, and were therefore considered objectively cured. By PGI, 77% (53/69) regarded themselves as cured, and 20% (14/69) as improved. No cases of tape erosion or adverse tissue reaction were observed.

The authors conclude that, in general, the TVT operation is beneficial and long-lasting when surgeons receive systematic training, and proper patient selection is performed. There was no distinct decline in cure rate over a period of 11 years.

Nilsson CG, Palva K, Aarnio R, Morcos RE, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. Published online: 06 April 2013, DOI 10.1007/s00192-013-2090-2.

This is a 17-year follow-up report of patients who received TVT slings reported by Ulmsten et al. 1998. Fifty-eight patients were evaluated; 12 by phone interview and 46 in the clinic. The mean follow-up was 16.9 years (range: 185-213 months). Of the 46 patients evaluated in the clinic, one had had a second surgery 15 years after initial tape placement due to recurrent SUI. Another patient, 69 years old, had a symptom-free para-urethral tape exposure for which local estrogen was prescribed. Objective cure, defined as a negative stress test, was seen in 42 of 46 patients (91.3%). Patient-reported quality of life outcomes showed that 87.2% of patients regarded themselves as cured or significantly improved.

At the 5-year follow-up (Nilsson, 2001), 90 patients were available for evaluation, versus 58 patients at the 17-year time point (64%). While not unexpected in this patient population, this lost-to-follow-up rate is greater than reported in the paper (22%). The authors observe that the risk of mesh complications after 17 years is negligible when using a monofilament polypropylene, large-pore mesh. They note that the complications associated with urogenital prolapse surgery that prompted the FDA Public Health and Safety Notifications in 2008 and 2011 may not have been caused by the mesh itself, but could be the result of improper training of the surgeon. They further note that the risk of complications, particularly tape material-related problems, appears to be small when the operation is performed according to the originally developed technique. Two authors (CGN, CF) have been paid consultants for Ethicon since at least 1999.

TVT STUDIES

Jeffry L, Deval B, Birsan A, Soriano D, Darai E. Objective and subjective cure rates after tension-free vaginal tape for treatment of urinary incontinence. Urology 2001;58:702-706.

This is a retrospective analysis of 112 consecutive women treated with the TVT procedure from June 1998 to February 2000 at a single hospital in Paris. Patients had urodynamically confirmed SUI ("genuine" incontinence, 78.6%) or mixed incontinence (includes bladder hyperactivity, 21.4%). A small percentage (6.2%) had had prior surgery for incontinence. Follow-up visits were scheduled at 1, 6, 12 and 24 months post surgery, and only patients with at least six months of follow-up were included in this report.

The overall complication rate was 37.5%. The perioperative complication rate was 14.3%, mostly due to bladder injuries, which occurred in 13 patients. The likelihood of bladder injury increased in patients with prior incontinence surgery. Other perioperative complications included excessive hemorrhage (> 300 mL), hemorrhage (< 300 mL), blood transfusion, and conversion to laparotomy. Early postoperative complications occurred in 32.1% of patients and included voiding difficulties lasting >15 days (12.5%), urinary infection (10.7%), urinary retention (8%), and abdominal wall hematoma (0.9%). Late postoperative complications occurred in 29.4% of patients and included de novo urge symptoms (25.9%), and voiding difficulties lasting >15 days (3.6%). No tape infections, erosions or healing defect of the vaginal wall occurred.

The overall objective cure rate was 89.3%, with no significant difference between the SUI and mixed groups (90.9% and 83.3%, respectively). The overall subjective cure rate was 66%, with 69.3% considered cured in the SUI group and 54.2% in the mixed group. This difference was also not statistically significant, possibly because of the small sample size.

The authors speculate that the rate incidence of bladder perforations seen in this study compared to other studies could be due to surgeons' level of experience, and also the higher risk of patients who had undergone prior incontinence surgeries. The subjective cure rate, also lower than previous reports, may have been due to differences in types of QOL scoring systems.

The authors conclude that TVT is a safe and effective procedure, but that patients should be informed of the risk of de novo urge symptoms that may impact their quality of life.

Tamussino KF, Hanzal E, Kolle D, Ralph G, Riss PA. Tension-free vaginal tape operation: results of the Austrian Registry. Am Coll Obstet Gynecol 2001;98(No. 5, Part 1):732-736.

The tension-free vaginal tape procedure introduced by Ulmsten and Petros quickly became popular despite the absence of comparative randomized trials. In 1998, the Austrian Working Group for Urogynecology initiated a registry of tension-free vaginal

tape procedures for the purpose of assessing the use of the operation and complications during surgery and the immediate postoperative period. This study reports the results of the TVT procedure in 2,795 patients from 55 centers in Austria.

The median age of the patients was 60 years (range:28-93). Of these, 2,022 had not undergone prior surgery for incontinence or pelvic organ prolapse. Overall, 1,640 procedures were TVT-only, and 1,155 were done in conjunction with other gynecologic procedures. The median operating time was 30 minutes (range: 10-120), regional anesthesia was used in 47% of cases, and local anesthesia used in 28% of cases. An indwelling urethral catheter was used for postoperative bladder drainage in 63% of cases.

There were a total of 75 bladder perforations (2.7%), and the rate was higher in patients who had had previous surgery for incontinence or pelvic organ prolapse (4.4% versus 2.0% in patients with no prior surgery). The median number of days until residual urine volume was less than 100 mL was one (range: 0->64) for TVT-only cases, and three after combination procedures. The overall rate of postoperative urinary tract infections was 17%. A total of 74 patients (2.6%) required reoperation during the postoperative period, most for reasons relating to the TVT procedure. Nineteen patients (0.7%) required reoperation for hematoma.

The authors conclude that, although there are considerable variations in clinical practice, major complications appear to be rare.

Bodelsson G, Henriksson L, Osser S, Stjernquist M. Short term complications of the tension free vaginal tape operation for stress urinary incontinence in women. BJOG 2002;109:566-569.

In this study, 177 patients underwent the TVT procedure for SUI at Malmo University Hospital, Malmo, Sweden. Three different surgeons performed the operations. Perioperative complications were recorded and patients had a follow-up visit 6-8 weeks later. Perioperative bladder or urethral perforation occurred in 26 patients (15%), with a disproportionate number attributed to one surgeon. Failure to void after catheter removal at 24 hours occurred in 35 patients and 21 underwent urethral dilation for persistent failure to void. There was also a significant difference between surgeons for these outcomes. Twelve patients (7%) developed cystitis during the 6-8-week postoperative period. Nine patients (6%) developed de novo urgency. Sling rejection occurred in three patients (1.7%). At the 6-8-week follow-up, 88% of patients reported complete continence, 11% reported improvement and 1% reported no change. There was no difference in success rates by surgeon performing the operation.

The authors conclude that short-term complications such as bladder perforation and urinary retention occurred at an unexpectedly high rate. They suggest that, while that might be related to the technique and experience of the surgeon, it is unlikely that these complications are unique to their practice.

Kuuva N, Nilsson CG. A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure. Acta Obstet Gynecol Scand 2002;81:72-77.

The objective of this study was to evaluate the therapy-associated morbidity of all patients who underwent a TVT operation in Finland by the end of 1999. Finland has a nationwide training program for this procedure, and systematically registers perioperative and immediate postoperative complications.

There are five university hospitals in Finland, one of which had been involved in the development of the TVT procedure. The latter hospital trained one experienced urogynecologist from each of the other four university clinics to perform TVT operations. The indications for performing the operation and the possible risks and complications were carefully explained to the trainees. The importance to register in detail preoperative and immediate postoperative complications was emphasized. First the trainees performed four to five operations together with the main instructor after which each trainee performed two operations alone under the guidance of the instructor. Later, the main instructor visited each of the four university clinics and observed how three to four operations were carried out by the local TVT team. A certificate to perform TVT operations was granted, if these operations went well. Finally each urogynecologist in each of the four university clinics had to perform 20 TVT operations and, if the results were good after a follow-up period of six months, they were authorized to teach other gynecologists in smaller hospitals within their own districts. In the end each central and local hospital in Finland had one certified TVT-surgeon and the university clinics possibly had several.

Included in this study were data from 38 hospitals that had been trained in the TVT procedure. The training hospital and another that did not use standard TVT equipment were excluded. Each participating hospital filled out a questionnaire that included number of TVT operations and number of the following complications: blood loss over 200 mL, bladder perforation, major vessel injuries, complete postoperative urinary retention, minor voiding difficulties, retropubic hematomas, wound infection, defective healing of the vaginal incision, urinary tract infection, tape rejection, and other postoperative complications.

A total of 1,455 TVT operations were performed during the study period. All patients were seen at a follow-up visit two weeks to two months postoperatively. The total incidence of complications was 206/1000 in university hospitals, 253/1000 in central hospitals, and 283/1000 in local hospitals. The most common perioperative complication was bladder perforation (3.8%), followed by blood loss > 200 mL (1.9%). The most common postoperative complication was voiding difficulty (7.6%), followed by urinary tract infection (4.1%). The incidence of major complications was 2.9/1000 in university hospitals, 2.1/1000 in central hospitals, and 4.7 in local hospitals. The TVT-associated complications considered major and requiring laparotomy, were one case each of arterial bleeding behind the symphysis (fibrocartilaginous joint), bladder perforation not detected

until Day 4, bladder perforation with unknown detection time, vesicovaginal fistula, and urinary retention.

The authors recommend performing a cystoscopy after every needle pass to detect bladder perforations immediately. They noted that one hospital that only performed cystoscopy at the end of the procedure had a high rate of bladder perforations and also of other complications. They conclude that TVT can be used with good results in different types of hospital provided that a systemic training program is first created and instructions are carefully followed. Good skills in cystoscopy are important.

Ward K, Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002;325:1-7.

This prospective, multicenter, randomized study compared TVT with colposuspension as primary treatment in patients with SUI. The trial was conducted at 14 gynecology or urology centers in the UK and Eire, including university teaching hospitals and district general hospitals. Included were patients with SUI who had completed their family. Exclusion criteria included detrusor activity, vaginal prolapse requiring treatment, previous surgery for prolapse or incontinence, and a major degree of voiding dysfunction, neurological disease or allergy to local anesthetic. All investigators underwent training in the TVT procedure (according to Ulmsten) prior to the start of the trial. Urodynamic assessments were performed at baseline, and patients completed a urinary diary for one week. In addition, a one-hour perineal pad test was performed. Patients' perceptions of changes in their symptoms and treatment outcome were measured with the generic SF-36 (a multi-purpose short form health survey), and the disease-specific Bristol female lower urinary tract symptoms questionnaire at baseline, six weeks, and six months after surgery. A complete assessment was performed in the clinics six months after surgery. The primary outcome measure was objective cure, defined as a negative stress test on urodynamic testing, and a negative one-hour pad test. Secondary outcome measures included subjective cure of incontinence, and the development of voiding problems, urge symptoms and vaginal prolapse.

Of 344 women enrolled, 175 were randomized to TVT and 169 to colposuspension. Operative complications were more common in the TVT group, largely due to injury of the bladder and vagina. Operation time, blood loss, analgesic requirements, postoperative complications, and catheterization were greater in the colposuspension group than the TVT group. Objective cure was found in 66% of TVT patients and 57% of colposuspension patients ($p = 0.099$). Both groups showed significant changes in most urinary symptoms at six months, and any differences were not statistically significant. At six weeks, the TVT group had improved significantly better than the colposuspension group in the SF-36 domains of emotional, social, physical function, and vitality. At six months, scores in the colposuspension group showed significantly less improvement in emotional and social functioning, vitality, and mental health than the TVT group. One patient in the TVT group had tape erosion, which was managed by partial excision and closure of the vaginal skin.

Although all investigators received training in the TVT procedure, they were from different medical backgrounds and had variable experience, so the group as a whole reflected current practice in the UK and Eire. The number of patients entered was less than the target recruitment, and therefore the study was underpowered. The objective cure rates for both procedures were lower than previously reported, possibly due to the strict definition of cure. Although patients in the TVT group reported a return to normal activity more quickly than patients in the colposuspension group, this finding may have been biased because patients were not blinded to treatment group, and those in the colposuspension group may have expected a longer convalescent period. The authors noted that cases of erosion are likely underreported in the literature and called for longer-term follow-up to quantify the extent of this complication (see Ward and Hilton, 2004).

Karram MM, Segal JL, Vassallo BJ, Kleeman SD. Complications and untoward effects of the tension-free vaginal tape procedure. Obstet Gynecol 2003;101:929-932.

This study reports the perioperative and long-term sequelae following the TVT procedure performed by one surgeon at a single center (Good Samaritan Hospital, University of Cincinnati Medical School) from November 1997 to November 2001.

The study included 350 consecutive patients with SUI. All underwent the procedure described by Ulmsten. This was the first SUI procedure for 280 patients, whereas 70 patients had undergone previous vaginal or retropubic procedures. Fifty-five percent of the patients had concomitant procedures besides the TVT.

There were a total of 19 bladder perforations in 17 patients (4.9%). Six patients developed postoperative hematoma, four of which were asymptomatic and resolved spontaneously. Seventeen patients (4.9%) had voiding dysfunction requiring intermittent self-catheterization > 7 days post surgery. Six of these patients subsequently underwent a take-down or cutting of the tape, with resolution of the voiding dysfunction. Two patients developed recurrent SUI; one underwent a retropubic colposuspension and the other received a transurethral injection of a bulk-enhancing agent. Twenty-eight women underwent one or more urethral dilations for various degrees of voiding dysfunction, of which 23 were cured or improved. Thirty-eight patients developed at least two urinary tract infections, and one patient was readmitted for urosepsis. Forty-two patients had persistent urgency and urge incontinence that required anticholinergic therapy beyond six weeks postoperatively. Three patients developed nerve injury or strain that was clinically apparent, all of which resolved within six weeks. Three patients had erosion or poor healing at the site of vaginal incision; one patient had a vaginal erosion trimmed with no recurrence, one patient with delayed healing was managed successfully with antibiotics and topical hormone treatment, and the third patient, whose SUI subsequently recurred, had a urethral erosion requiring tape excision.

The authors conclude that TVT is an efficacious procedure in their hands, and feel that it is safe when performed by experienced surgeons.

Ansquer Y, Marcollet A, Yazbeck C, Salomon L, Poncelet C, Thoury A, et al. The suburethral sling for female stress urinary incontinence: a retropubic or obturator approach? J Am Assoc Gynecol Laparoscopists 2004;11:353-358.

At the time this study was published, the TVT procedure was considered the first-line surgical treatment for SUI. However, due to the bladder and less frequent but serious bowel and vessel injuries that can be caused with this type of procedure, this study was undertaken to compare the results of TVT and obturator (TVT-O) approaches. From January 2, 2001 through January 31, 2002, 49 patients underwent sling placement for SUI. From January 2001 through September 2001 the TVT approach was used (25 patients) and from October 2001 through January 2002 the TVT-O approach was used (24 patients). Patient characteristics in the two groups did not differ. Urodynamic evaluations were available for 21 patients in the TVT group, and 20 patients in the TVT-O group. Patients were considered to have mixed incontinence when uninhibited detrusor contractions were observed. The postoperative evaluation at one month was performed by the surgeon. Patients were considered cured if they declared themselves to be dry, and if no incontinence on stress provocation test was found. Patients were considered to be improved if they reported less leakage than before surgery and showed no incontinence by stress test.

No serious intraoperative complications were observed. One case of bleeding occurred in the TVT-O group, but required no transfusion. However, six days after surgery, this patient was readmitted after vaginal dehiscence due to a hematoma of the vaginal wall. The suture was replaced under local anesthesia, and follow-up was uneventful. Two patients in the TVT group and no patients in the TVT-O group experienced bladder injuries. One patient had a bilateral injury: she was discharged on Day 3 and the bladder catheter was removed on Day 10. The other injury was unilateral: the patient was discharged on Day 1 and the bladder catheter was removed on Day 5. Voiding difficulties were significantly more frequent in the TVT group (10 patients versus two patients in the TVT-O group). All but two (both in the TVT group), resolved within a week. Two patients in the TVT-O group experienced dehiscence, compared with none in the TVT group. In the TVT group, at the one-month follow-up, 80% of patients were cured, and another 20% substantially improved. In the TVT-O group, 83% of patients were cured, and 13% substantially improved.

The authors note that, in the TVT approach, the sling kinks the urethra, which may account for the voiding difficulties, whereas in the TVT-O approach, the sling is positioned almost horizontally. However, they also note that this lower risk may be correlated with lesser efficacy. This study showed similar results for immediate risks, but the long-term results were not studied. It is also worth mentioning that performing all of the TVT procedures first could have introduced bias into the results. The authors recommend a randomized trial to compare the two approaches.

Ward KL, Hilton P. A prospective multicenter randomised trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: Two-year follow-up. Am J Obstet Gynecol 2004;190:324-331.

This article reports 2-year follow-up data from the study described in Ward and Hilton 2002. The primary outcome measure for the 2-year assessment was cure of SUI based on a negative 1-hour pad test. A negative 1-hour pad test was recorded for 111 (81%) patients in the TVT group and 86 (80%) patients in the colposuspension group. If the data are analyzed ignoring withdrawals, there was no significant difference between groups. If withdrawals were treated as treatment failures, the TVT group was statistically significantly better than the colposuspension group (cure rate 63% versus 51%, respectively; p = 0.02). Most urinary symptoms had improved significantly in both groups at two years, with no significant differences between groups except for a lower incidence of daytime frequency in the TVT group. In SF-36 domains, patients in the colposuspension group had significantly lower scores in emotional role and mental health than the TVT group. Rates of reoperation for SUI did not differ significantly between the two groups after two years (three patients in the TVT group and five patients in the colposuspension group). A significantly higher number of patients in the colposuspension group underwent surgery for uterovaginal prolapse during the follow-up period, and a higher proportion of women in this group were still self-catheterizing at two years.

The authors conclude that TVT is as effective as colposuspension for the treatment of SUI after two years.

Abouassaly R, Steinberg JR, Lemieux M, Marois C, Gilchrist LI, Bourque J-L, et al. Complications of tension-free vaginal tape surgery: a multi-institutional review. BJU Int 2004;94:110-113.

In this retrospective multi-institutional review, 241 patients who had had a TVT (Ulmsten method using Ethicon polypropylene mesh tape fixed to six needles) procedure performed at six hospitals (two university and four community) were reviewed by a single urologist and analyzed for complications during and after surgery. Data collected included age, parity, previous incontinence/pelvic surgery, comorbid conditions, pad score (number of pads used per day), and use of hormone replacement therapy. Preoperative evaluation included a physical examination for the presence of associated pelvic organ prolapse,, urethral hypermobility, and atrophic vaginal changes. Multichannel urodynamic testing was available for 198 patients.

Mean follow-up was 147 days (range: 60-484). Twenty-two women had other pelvic procedures performed concomitantly. Intraoperative complications included blood loss >250 mL (13 patients, 5.4%), and bladder perforation (14 patients, 5.8%). Post-surgical complications included urinary retention (47 patients), with most in retention for <48 hours (32 patients, 68%), and 32% (15 patients) for >48 hours. Four patients with long-term retention improved spontaneously, seven required TVT release, and three required sectioning of the TVT. Pelvic hematoma occurred in 1.9% of patients, only one of whom

required surgical drainage. One patient had a suprapubic wound infection that was treated with antibiotics.

At the 1-year follow-up, there were 33 cases of de novo urge (13.6%), but the patients remained continent. Fourteen patients complained of urgency and/or frequency. Thirty-four patients complained of minor difficulty voiding, and 15 reported mild, persistent suprapubic discomfort. Twenty-five patients reported at least one urinary tract infection within three months after surgery. Two patients experienced tape erosion through the vaginal mucosa, requiring removal of 2 cm of tape beneath the urethra. In both cases, there was complete vaginal healing with no sign of infection or erosion at a 6- to 8-week follow-up.

The authors conclude that their results showed a slightly higher complication rate than had been reported previously with this procedure; however, they felt that their results may better reflect the morbidity of TVT insertion in clinical practice. The TVT procedure is minimally invasive, effective and safe technique for treating SUI.

Flock F, Reich A, Muche R, Kreienberg, Reister F. Hemorrhagic complications associated with tension-free vaginal tape procedure. Obstet Gynecol 2004:104:989-994.

Between August 1998 and August 2003, 336 patients had undergone the TVT procedure at a single institution (University of Ulm, Ulm, Germany). This paper reports the incidence, short-term and long-term sequelae, and clinical management of bleeding complications associated with TVT.

Intraoperative blood loss > 200 mL occurred in seven patients (2.1%), with an uncomplicated postoperative course. Fourteen patients (4.1%) developed retropubic hematoma. Five of these patients (hematoma volume <100 mL) had minor symptoms or none. Patients with hematomas > 100 mL in volume had moderate (six patients) or severe (three patients) pain. Four patients with a hematoma ≥ 300 mL required surgical removal of the hematoma. Complete resolution in all patients was confirmed after two to five months. All but one of the patients with hematoma were completely continent 10 weeks after surgery.

The authors speculate that most hematomas are caused by injury of the perivesical plexus. They conclude that retropubic hematoma is a rare but typical complication of TVT surgery, occurring in 1-4% of cases. Whereas most hematomas do not require intervention, evacuation is indicated in hematomas > 300 mL.

Paraiso MF, Walters MD, Karram MM, Barber MD. Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial. Obstet Gynecol 2004;104:1249-1258.

This was a prospective, randomized, comparative trial of Burch colposuspension versus TVT for the treatment of SUI. Seventy-two patients were recruited from August 1999

through August 2002, and followed through January 2004. Evaluations included standard history, gynecologic exam, neurologic exam, urinalysis, and urodynamic evaluation. The primary outcome measure was objective cure, defined as no evidence of leakage during urodynamic studies. Secondary outcomes included subjective continence, hospital data and cost, complications, time to achieve normal voiding, data from pelvic organ prolapse quantification and cotton-tipped swab examinations, urinary diaries, sexual function, and quality of life.

Demographic data were similar between groups. The only statistically significant difference in concomitant procedures was that 32% of patients in the Burch group underwent lysis of adhesions, compared to 11% of the TVT group. The Burch group had a significantly longer operating time. Estimated blood loss, change in hematocrit, analgesia requirement, hospital stay, total hospital costs, and number of days to normal voiding were similar between groups.

Complications were not significantly different. One patient in the TVT group required an intraoperative blood transfusion, and there were two cystotomies in the TVT group. One patient in the Burch group had a bowel injury. Postoperative complications included one hematoma and one abscess in each group. One patient in the Burch group suffered from postoperative ileus, and one was admitted one week post surgery for pulmonary embolism. One patient in the Burch group was readmitted for pyelonephritis. Two patients in the Burch group underwent subsequent collagen injection. One patient in the TVT group had vaginal mesh erosion, which was managed conservatively. Two patients in the TVT group required mesh transection for voiding dysfunction.

Both groups had statistically significant improvements in number of incontinence episodes, weekly pad use, and percentage using pads at one and two years after surgery. There was no statistically significant difference between groups for these parameters. Patient satisfaction was high in both groups at one and two years after surgery, and was also not significantly different between groups. There was a greater rate of urodynamic stress incontinence in the Burch group (18.8%) than the TVT group (3.2%). Voiding dysfunction, pelvic organ prolapse quantification and cotton-tipped swab examination were also similar between groups. Time to development of symptoms for stress and urge incontinence was significantly shorter for the Burch group.

The authors noted that the sample size of this study was small. Originally, they intended to enroll 130 patients to detect a 20% difference in continence rates with 80% power and a significance level of 0.05. However, due to lack of funding and slow recruitment, the trial was stopped early.

The authors conclude that TVT resulted in greater objective and subjective cure rates than the laparoscopic Burch procedure.

Ward KL, Hilton P. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5 year follow up. BJOG 2008;115:226-233.

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This article reports 5-year follow-up data from the study described in Ward and Hilton 2002. The primary outcome measure for the 2-year assessment was cure of SUI based on a negative 1-hour pad test. Secondary outcome measures were subjective cure and development of urgency (measured with the Bristol Female Lower Urinary Tract symptoms [BFLUTS] questionnaire), and vaginal prolapse. Of 316 women who were treated with either TVT sling (n = 170) or colposuspension (n = 146), 98 in the TVT group and 79 in the colposuspension group participated in the 5-year follow-up. Of these, 26 and 30, respectively, provided questionnaire data only.

Of women who received objective assessments, 58/72 in the TVT group (81%) and 44/49 in the colposuspension group (90%) had negative pad tests. Incontinence symptoms had improved from baseline in both groups. The number of women reporting cure of stress leakage was 63% in the TVT group and 70% in the colposuspension group. Overall, women who regarded themselves as satisfied or very satisfied with their procedure was 91% in the TVT group and 90% in the colposuspension group. Both groups showed a reduction in cystocele after 5 years compared to baseline, and both groups showed an increase in enterocele or vault/cervical prolapse and rectocele after 5 years. The percentage of women with enterocele or vault/cervical prolapse and rectocele was statistically significantly higher in the colposuspension group than the TVT group. Two vaginal tape erosions had occurred since the 2-year follow-up and one erosion into the bladder had occurred.

The lost to follow-up rate was more than 40% in both groups, including women who only completed questionnaires. The authors note that they cannot be certain that data are missing at random and the possibility exists that withdrawal or loss to follow-up may be related to outcome. Further, conclusions regarding the effectiveness of either procedure are heavily dependent on the handling of missing data and assumptions about withdrawals or missing data. However, within these limitations, the authors conclude that TVT appears to be as effective as colposuspension for the treatment of SUI at 5 years, and both procedures have long-term benefits. This article shows that tape erosion may occur years after surgery.

Barber MD, Kleeman S, Karram MM, Paraiso MF, Walters MD, Vasavada S, et al. Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence. Obstet Gynecol 2008;111:611-621.

In the decade after the TVT procedure was introduced in 1996, it became a popular method of treating SUI, and was considered the gold standard by some surgeons.

However, despite its proven efficacy, it was also associated with rare but serious, and in some cases life-threatening, complications. The blind retropubic passage of trocars from the vagina to the abdomen is unique to TVT and is associated with a 3-9% bladder perforation rate and, rarely, bowel and major vascular injuries. The transobturator mid-urethral sling was described in 2001. The purpose of this approach was to reduce the risk of bladder, bowel and iliac vessel injury. Subsequent meta-analyses confirmed this, but failed to show superior efficacy with either procedure. The objective of this prospective, randomized, multicenter comparative study was to test the hypothesis that transobturator tape is not inferior to TVT in the treatment of SUI in patients with and without concurrent pelvic organ prolapse.

Eligible patients had urodynamically confirmed SUI, were at least 21 years old and desired surgical correction of their incontinence. Exclusion criteria included detrusor overactivity; postvoid residual volume > 100 mL; history of previous sling procedure; desired future childbearing; history of hidradenitis suppurativa, inguinal lymphadenopathy or an inguinal or vulvar mass; history of bleeding diathesis or currently on anticoagulation therapy; current genitourinary fistula or urethral diverticulum; or otherwise had a contraindication for surgery. Baseline evaluations included urogynecologic history, POP-Q staging, cotton-tipped swab test of urethral mobility, and a urodynamic evaluation. Additionally, participants completed the Incontinence Severity Index (ISI), Pelvic Floor Distress Inventory, Short Form-20 (PFDI-20), Pelvic Floor Impact Questionnaire, Short Form-7 (PFIQ-7), the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, Short Form (PISQ-12), the Medical Outcomes Study Short Form (SF-12), and a 3-day bladder diary. All study surgeons had substantial experience with TVT and had performed at least ten transobturator procedures. TVT procedures were performed “bottom up”, as described by the manufacturer (Gynecare, Ethicon) and transobturator procedures were performed out-to-in (AMS Monarc). The transobturator procedure will therefore be referred to as TOT, to distinguish it from the TVT-O (in-to-out) technique. Patients were followed 6 weeks and 6, 12, 18 and 24 months after surgery. Patients were also contacted on postoperative days 1, 3, and 7 and asked to rate their pain on a 10-point verbal numeric pain scale, and to document their use of pain medication during the previous 24 hours.

The primary outcome was the presence or absence of abnormal bladder function, a composite endpoint defined as the presence of any of the following: 1) incontinence symptoms of any type, 2) positive cough stress test, 3) retreatment for SUI, or 4) postoperative urinary retention.

Between November 2004 and January 2006, 170 patients were randomized (TVT: 88; TOT: 82). Seven percent of patients had undergone a previous incontinence procedure, and 20% had vaginal or uterine prolapse. Sixty-one percent of patients had concomitant surgeries performed in addition to TVT or TOT. Overall, intraoperative complications occurred more often in the TVT group (9% versus 1%, $p = 0.02$). This was attributed to a difference in bladder perforations. Otherwise, the incidence of intraoperative complications was similar between the two groups. Median pain scores and use of narcotic pain medications on Days 1, 3, 7 or at six weeks were not significantly different

between groups. Mesh erosions occurred in five TVT patients and one TOT patient. No leg or obturator complications occurred in either group during the perioperative period, but two patients in the TVT group and three in the TOT group reported leg pain or difficulty ambulating during follow-up.

Abnormal bladder function occurred in 46.6% of TVT patients and 42.7% of TOT patients. Therefore, according to the study design, TOT is not inferior to TVT. SUI symptoms were reported postoperatively in 15% of each treatment group, with 13% in the TVT group and 12% in the TOT group classifying these symptoms as bothersome.

New or worsened urge incontinence was noted after surgery in 10% of the TVT group and 4% of the TOT group. Overall, the median number of incontinence episodes per day, and pads used per day recorded on the bladder diary, decreased from 2.3 (range 0 to 16.3) to 0 (range 0–11) and from 1.3 (range 0 to 7.6) to 0 (range 0 to 6.3), respectively, with no differences between groups. One year after surgery, 79% of participants in the TVT group and 82% of participants in the TOT group reported that their bladder symptoms were either "much better" or "very much better" on the PGI-I. There was no significant difference in the median time to development of postoperative incontinence symptoms between the two groups (19.1 months for TVT compared with 20.1 months for TOT). There was significant improvement of quality of life scores in both groups, with no statistically significant differences between groups.

The authors conclude that the Monarc transobturator tape is not inferior to TVT for the treatment of SUI in women with or without pelvic organ prolapse with one to two years of follow-up. Transobturator tape procedure results in fewer bladder perforations than TVT; however, the clinical significance of a bladder perforation after TVT is unclear. In each instance of perforation in this study, the perforating trocar was merely removed and replaced outside of the bladder without consequence. Other perioperative complications are similar between the two procedures. Larger studies are needed to evaluate the relative risk of the less common but potentially severe complications that have been seen with both procedures. Studies with longer follow-up are necessary to determine if the efficacy of transobturator tape is durable.

Jelovsek JE, Barber MD, Karram MM, Walters MD, Paraiso MFR. Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow-up. BJOG 2008;115:219-225.

[Supplemental article to Paraiso et al., 2004]

The original study was designed to compare the efficacy of Burch colposuspension with the TVT procedure for treatment of SUI. At the 1-year follow-up, there was a higher rate of urodynamic stress incontinence in the Burch group (18.8%) than the TVT group (3.2%). This study reports long-term outcomes: the median duration of follow-up was 65 months (range: 12-88 months). Subjects were contacted by phone to assess subjective urinary incontinence, quality of life, and overall improvement. The primary outcome was

the subjective cure of any urinary incontinence as measured by the validated Incontinence Severity Index (ISI).

Twenty-five patients in the TVT group and 28 patients in the Burch group were able to be evaluated in this long-term study. Forty-eight percent reported any urinary incontinence and 8% reported bothersome SUI in the TVT group, compared to 57% and 11%, respectively, in the Burch group. These differences were not statistically significant. Time to development of any incontinence symptoms was 52 months in the Burch group and 87 months in the TVT group (not significantly different). Seventy-two percent of subjects in the Burch group and 68% in the TVT group reported they were "much better" or "very much better" compared with before their surgery, while 7% and 4% reported they were "much worse" or "very much worse" on the PGI-I. Eighty-eight percent of subjects in the Burch group reported that if they had to do it all over again, they would choose the same treatment versus 79% in the TVT group. Only 4% of subjects in both groups underwent reoperation for SUI at some point during the follow-up period. Overall, 25% of subjects were using pads postoperatively for urinary leakage, and approximately 10% of subjects were taking anticholinergic medication with no significant differences between groups. Quality of life significantly improved on the UDI-6 and IIQ-7 in both groups one to two years after surgery with no differences between groups. This improvement was maintained throughout the length of follow-up.

The authors conclude that TVT has similar long-term efficacy to laparoscopic Burch for the treatment of SUI. A substantial proportion of subjects have some degree of urinary incontinence four to eight years after surgery; however, the majority of incontinence is not bothersome.

An editorial commentary on this paper notes that the study was underpowered.

Amaro, JL, Yamamoto H, Kawano PR, Barros G, Gameiro MOO, Agostinho AD. Clinical and quality-of-life outcomes after autologous fascial sling and tension-free vaginal tape: A prospective randomized trial. Int Braz J Urol 2009:35:60-67.

In this prospective, randomized trial, the TVT procedure (Ulmsten) was compared with an autologous fascial sling procedure in which a strip of the patient's rectus fascia was used to support the urethra. Patients with SUI were randomly assigned to treatment groups. Patients with involuntary detrusor contractions or preexisting bladder outlet obstructions were excluded. Clinical follow-up and subjective success rate evaluations were performed at 1, 6, and 12 months after surgery, and then annually. A questionnaire was used to obtain personal data, obstetric, gynecologic, family medical history, and subjective analysis of urine loss. Cure was defined as complete dryness with no usage of pads as reported by the patient. Cure rate, long-term patient satisfaction, and impact on quality of life (validated King's Health Questionnaire) were assessed at 36 months.

No statistically significant differences in demographic data and urodynamic parameters between groups were found. Operative time was significantly shorter with TVT. There were no differences between groups in bladder injuries, hospitalization time,

postoperative catheterization or return to normal activities. Neither group had prolonged urine retention or other complications. There were no significant differences in cure rates between the groups at any evaluation time points, as shown in the following table.

Comparative cure rates between TVT and autologous fascial sling, %		
Months post surgery	TVT N = 20	Autologous sling N = 21
1	75	71
6	70	57
12	65	57
36	63	55

The postoperative satisfaction rate was 58% for TVT and 80% for autologous repair ($p > 0.05$). De novo urgency symptoms were observed in 42% of TVT patients and 40% of autologous repair patients. There were no significant differences in quality of life between the two groups. The authors conclude that TVT and autologous repair yielded similar results, except for a longer operating time for autologous repair.

Editorial response to the article

A critique of this article included the following: 1) the impact of urinary incontinence of quality of life was not measured preoperatively, and therefore the degree of improvement after surgery is unknown, 2) postoperative pain was evaluated by the dosage of analgesics delivered, rather than with a patient-reported test such as visual analog scale, 3) the small sample size may have been the reason that no statistical differences were observed, and 4) no cost analysis was performed to determine whether the additional time in the operating room required for the autologous procedure was counteracted by the cost of the TVT sling. The editor called for additional randomized studies.

Richter HE, Albo ME, Zyczynski HM, Kenton K, Norton PA, Sirls LT, et al. Retropubic versus transobturator midurethral slings for stress incontinence. NEJM 2010;362:2066-2076.

This article presents the 12-month follow-up data from the TOMUS trial, a prospective, randomized trial that compared efficacy and safety of the retropubic mid-urethral sling (TVT) procedure with the transobturator mid-urethral sling[1] (see Brubaker et al. 2011 and Albo et al. 2012). The primary outcome measures were 1) objective treatment success at 12 months, as measured by negative stress test, negative pad test, and no retreatment for stress urinary incontinence (SUI) including behavioral, pharmacologic or surgical procedures; and 2) subjective treatment success at 12 months, defined as the absence of self-reported symptoms of stress-type urinary incontinence, as assessed with the use of the Medical, Epidemiological and Social Aspects of Aging (MESA) questionnaire (responded "never" to all nine MESA questions), no leakage recorded in a 3-day voiding

[1] TVT-O: Choice of Gynecare Tension-free Vaginal Tape using in-to-out placement or AMS Monarc using out-to-in placement.

diary, and no retreatment for stress incontinence including behavioral, pharmacologic or surgical treatment. Secondary outcome measures included 3) patient satisfaction at 12 months, defined as completely or mostly satisfied with the surgery, 4) change in quality of life from baseline to 12 months, and 5) bother as measured by the Urogenital Distress Inventory (UDI) at 12 months.

Of 597 patients randomized, 565 (94.6%) completed the 12-month assessment. Baseline demographic and clinical characteristics were similar between the TVT and TVT-O groups. Unadjusted objective satisfaction rates were 80.8% for the TVT group and 77.7% for the TVT-O group. Unadjusted subjective treatment success rates were 62.2% for the TVT group and 55.8% for the TVT-O group. Adjusting for site or for Valsava leak-point pressure did not materially change the results.

Bladder perforations from trocar passage, and voiding dysfunction requiring surgical intervention were uncommon, but occurred only in the TVT group; women in this group were also more likely than women in the transobturator-sling group to have a higher (100 mL or more) residual volume after voiding at the time of discharge from the hospital (P=0.02), and to have postoperative urinary tract infections (P=0.04). More vaginal perforations occurred in the TVT-O group than in the TVT group (13 versus 6); the majority of those in the TVT-O group occurred when the in-to-out approach was used. The frequency of neurologic symptoms was also higher in the TVT-O group than in the TVT group (P=0.01); weakness in the upper leg was the most common neurologic symptom, occurring in 24 (60%) of those who reported neurologic symptoms.

The rates of patient satisfaction with the treatment were similar between the TVT group and the TVT-O group (85.9% and 90%, respectively; P=0.14). There were no significant differences between the groups in changes between baseline and postoperative "distress"

and "bother" scores (which measure the distress caused by symptoms of urinary incontinence, and the degree to which the woman is bothered by those symptoms) or the effect of these symptoms on quality of life.

The authors conclude that objective success rates for the two treatments showed equivalence and, while similar, the subjective success rates were not equivalent, with a higher subjective success rate in the TVT group. Differences in the complications associated with the two procedures should be discussed with patients considering SUI surgery.

Brubaker L, Norton PA, Albo ME, Chai TC, Dandreo KJ, Lloyd KL, et al. Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study. Am J Obstet Gynecol 2011;205:498e1-e6.

The TOMUS trial was a prospective, randomized trial that compared efficacy and safety of the retropubic mid-urethral sling (TVT) procedure with the transobturator mid-urethral

sling (TVT-O and Monarc) procedure. This article is a report of 2-year adverse event experience of women enrolled in the TOMUS trial.

Uniform definitions of adverse events (AEs) were established before the trial, and each AE was reviewed by a Complications Working Group. A total of 597 patients were randomized to treatment, 298 to the TVT group, and 299 to the TVT-O group. Five hundred twenty-eight patients completed the 24-month assessments, or failed treatment at or before that visit. Over the 24-month period, 42% of patients experienced at least one AE, and 12% experienced a serious AE (SAE). Most AEs had an onset date within six weeks after surgery. Patients were more likely to experience an AE if they reported prior urinary tract infection (UTI), prior continence surgery, experienced longer surgical times or increased blood loss. SAEs included bladder perforation, urethral perforation, pulmonary embolus, postoperative bleeding, mesh erosion, mesh exposure, deep incisional surgical site infection, organ/space surgical site infection, recurrent urinary tract infection, neurologic symptoms, granulation tissue, vaginal epithelium perforation, voiding dysfunction requiring surgery or catheter use, and other (not specified).

Intraoperative bladder perforation occurred only in the TVT group. Intraoperative blood loss was the second most common intraoperative AE in both groups and occurred twice as frequently in the TVT group. Fifty-three neurologic AEs were reported, including one SAE. Neurologic AEs were more common in the TVT-O group, regardless of whether concomitant surgery was performed. Most symptoms were mild and had resolved by six weeks post surgery; however, at two months, four remained unresolved.

Concomitant surgery increased the overall occurrence of AEs (although not of SAEs). UTIs were common, accounting for 25.8% of all AEs (TVT 16.7%, TVT-O 9.1%). Patients in the TVT group also had a higher rate of voiding dysfunction, which may be related to the incidence of UTI.

The authors state that, because the efficacy is similar for the two procedures (see Richter et al. 2010 and Albo et al. 2012), the AE profile may be used to counsel patients and choose an appropriate procedure.

Hamer MA, Larsson P-G, Teleman P, Eten-Bergqvist, Peterson, J. Short term results of a prospective randomized evaluator blinded multicenter study comparing TVT and TVT-Secur. Int J Urogynecol 2011;22:781-787.

The TVT-Secur (Gynecare, Ethicon) was introduced in Europe in 2006. The goal was to reduce the complications associated with the passage of the needle through the retropubic or obturator areas. This was to be accomplished by the use of a short sling with high friction resorbable ends placed either in the retropubic soft tissue or the obturator muscle without passing any further. This study was designed to compare the TVT-Secur with the retropubic TVT for efficacy and safety in a prospective, randomized, multicenter trial.

From 2007 through 2009, patients were screened for inclusion in the study. Inclusion criteria were history of SUI, wish for surgical treatment, no future pregnancies planned,

age ≥ 18 years, ≥ 3 mL leakage in a standardized pad test, and cough-synchronous leakage at stress test. Exclusion criteria included need for concomitant surgery for genital prolapse, undergoing less than three months of genital floor training, planned or current pregnancy, prior surgery for urinary incontinence, bladder capacity < 300 mL, residual urinary volume > 100 mL, known detrusor instability, cystitis > four times during the previous 12 months, pyelonephritis > one time during the previous five years, known or suspected neurological conditions, current anticoagulation therapy which could not be interrupted in due time prior to surgery, patients with known abnormal coagulation, allergy to local anesthetics and/or metronidazol, and cognitive or language problems precluding comprehension of written study information or questionnaires.

Six surgeons with at least 100 suburethral sling operations participated in this study. Pre-study training was supervised by one of the authors and consisted of at least five TVT-Secur procedures and aimed to standardize operative technique before enrolling patients into the study. All patients were operated on an ambulatory basis following the techniques for TVT and TVT-Secur as recommended by the manufacturer. Postoperative counseling of patients as well as the extension of sick leave were standardized and prescribed solely on an occupational basis and in an identical way for both groups (three to seven days for sedentary work and up to two weeks for more physically exerting work). In addition, all patients received written information to avoid gymnastics/work, bicycling, and sexual intercourse for four weeks after surgery. Follow-up consisted in a standardized telephone interview two months after surgery, an outpatient examination one year after surgery including the pad-test, stress test, VAS scale and King's health questionnaire, and voiding diary used before surgery. The follow-up was performed by an independent evaluator, usually a urotherapist. The evaluator blinding was achieved by placing the patient' s operative file as well as the results of the randomization in a sealed envelope immediately after surgery, and by instructing the patient not to reveal the operative technique at any subsequent follow-up.

A total of 125 women were treated, and 123 had 2-month follow-up data. Two patients in the TVT group had voiding difficulties > 24 hours. Two patients in the TVT-Secur group needed intermittent catheterization for more than 24 hours (two and seven days, respectively). No patients experienced permanent obstructed voiding. No tapes had to be loosened or cut postoperatively. Six minor perioperative complications were reported: two bladder perforations, both with TVT, two accidental perforations of the vaginal wall beside the incision (one with TVT-Secur, and one with TVT), one venous bleeding of about 200 mL with TVT, which was solved with compression, and one bleeding between 100 and 200 mL with TVT-Secur.

Three major complications occurred, all following the TVT-Secur procedure. One patient had an injury of the corona mortis, which required immediate surgical reintervention with evacuation of a one liter retropubic hematoma and vessel ligature. In another patient, tape erosion into the urethra was diagnosed 70 days after surgery. After an initial expectant management, the sling that subsequently had eroded further into the urethra, was removed by ureteroscopy 22 months after surgery resulting in an SUI recurrence. A third patient presented soon after surgery with recurrent bacteriuria and urgency symptoms.

Cystoscopy revealed the distal end of the TVT-Secur sling inside the bladder at one side. The intracystic part of the sling was removed by a combined endoscopic and cystoscopic procedure.

At the postoperative telephone follow-up (TVT group median 75 days (range 36-242 days), TVT-Secur group median 79 days (range 30-227 days) the subjective cure rate, defined as cured or improved, for stress incontinence symptoms was 92% for TVT and 72% for TVT-Secur, (p-0.01). Due to the significantly lower subjective cure rate in the TVT-Secur group and the three serious complications, enrollment was stopped early.

The authors discourage further use of the TVT-Secur.

Albo ME, Litman HJ, Richter HE, Lemack GE, Sirls LT, Chai TC, et al. Treatment success of retropubic and transobturator mid urethral slings at 24 months. J Urol 2012;188:2281-2287.

This article presents the 24-month follow-up data from the TOMUS trial, a prospective, randomized trial that compared efficacy and safety of the retropubic mid-urethral sling (TVT) procedure with the transobturator mid-urethral sling[2] (see Brubaker et al. 2011 and Richter et al. 2010).

Of 597 patients randomized, 516 (86.4%) were assessed at 24 months. The unadjusted objective success rate was 77.3% in the TVT group and 72.3% in the TVT-O group. The unadjusted subjective success rate was 55.7% in the TVT group and 48.3% in the TVT-O group. These results did not meet the criteria for equivalence; however, because the statistical confidence intervals all included zero, the rates cannot be considered different from one another. Adjusting for site, concomitant surgery, Valsalva leak point pressure or maximal urethral closure pressure did not significantly change the success rates. Patient satisfaction rates at 24 months were 86.3% in the TVT group and 88.1% in the TVT-O group, although there was a higher percentage of patients in the TVT-O group than the TVT group who reported being much or very much better according to the Patient Global Impression of Improvement questionnaire (91.5% versus 86.8%, respectively).

Safety data were reported elsewhere by Richter et al. and will not be repeated here.

The authors conclude that objective success rates, while meeting the criteria for equivalence at 12 months, no longer did so at 24 months (higher success in TVT group, with the caveat that confidence intervals included zero). Subjective success comparison remained inconclusive. Patient satisfaction was high and symptom severity markedly improved. Continued surveillance is important in patients undergoing SUI surgery.

[2] TVT-O: Choice of Gynecare Tension-free Vaginal Tape using in-to-out placement or AMS Monarc using out-to-in placement.

Funk MJ, Siddiqui NY, Kawasaki M, Wu JM. Long-term outcomes after stress urinary incontinence surgery. Obstet Gynecol 2012;120:83-90.

This study used the Thomson Reuter MarketScan Commercial Claims and Encounters database (heal care claims) to estimate the long-term rate of reoperation for SUI from 2000 to 2009. The secondary objective was to identify predictors of time to repeat SUI surgery. This database includes data from approximately 100 employer-based health plans in the US and is therefore weighted to the younger, non-Medicare, privately insured population. SUI procedures were captured based on CPT codes.

A total of 32.9 million women were in the database, of which 168,844 underwent one or more SUI procedures. The first procedure was identified for all patients and the median follow-up was 1.3 years (range: 0-9.75). The cumulative incidence of repeat SUI surgery for all types of surgery at nine years of follow-up was 14.5%. The type of repeat surgery performed was sling (70.5%) followed by bulking agents (20.1%), Burch (6.5%), laparoscopic (1.5%), needle (0.8%), total vaginal hysterectomy (0.5%), and Kelly (0.2%). As expected, bulking agents had the highest incidence of repeat surgery followed by needle suspension; the Burch procedure had the lowest incidence, which was 10.8% at nine years of follow-up. Because the rate of repeat surgery for bulking agents was so high, the incidence of repeat surgery after excluding this procedure was also estimated. With bulking agents excluded, the cumulative incidence of repeat SUI surgery remained unchanged at 14.5%, which reflects the fact that bulking agents represented only a small fraction of the total number of surgeries.

Women aged 35 to 44 years and 45 to 54 years did not have a significant difference in rate of repeat surgery compared with women aged 18 to 34 years. However, women aged 55 to 64 years had a 14% higher rate of repeat surgery compared with women aged 18 to 34 years. Compared with women who had the index surgery in 2000, the rate of repeat surgery was significantly lower in all subsequent years (2001–2009). When compared with the Northeast region of the United States, the rate of repeat surgery was elevated in the South and in the West but was not significantly different in the Midwest. After adjusting for age, calendar year of index surgery, and region, the rate of repeat surgery was 8-fold higher for bulking agents compared with Burch. For slings, the rate of repeat surgery was 28% higher than the rate for Burch.

Limitations of this study include the fact that the database would not capture surgeries for SUI that were performed before enrollment in a participating health plan. Also, the database does not capture information for older women, who are an important population for SUI surgery. CPT codes do not distinguish between mid-urethral mesh slings and traditional bladder neck or pubovaginal slings, nor do they distinguish between the different types of mid-urethral slings (retropubic, transobturator, mini-slings).

The authors conclude that further research is needed to evaluate other factors that may explain the differences in the rate of repeat SUI surgery between the Burch procedure and slings. However, based on these data, the Burch procedure remains an effective surgery

for SUI with the lowest risk of reoperation in women aged 18-64.

Nguyen JN, Jakus-Waldman SM, Walter AJ, White T, Menefee SA. Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. Obstet Gynecol 2012;119:539-546.

This was a retrospective analysis of complications occurring after placement of synthetic implants for vaginal prolapse or SUI. The study cohort comprised all female members of Kaiser Permanente Southern and Northern California and Hawaii who underwent prolapse or sling procedures between September 1, 2008 and May 31, 2010. Eligible patients were identified by searching appropriate CPT codes (Current Procedural Terminology, AMA). This summary is restricted to SUI complications.

A total of 3,748 sling procedures were reported. Trocar bladder perforations occurred more commonly than urethral perforations and occurred more often with retropubic (2%) than transobturator (0.5%) slings. Sling loosening or transection for voiding dysfunction or urinary retention occurred in 49 (1.3%) procedures overall. Excision for vaginal mesh erosion occurred in 30 (0.8%) procedures at a mean of 175 days (range: 46-388) after index procedure. Excision rates did not differ significantly between sling approaches.

The authors note that, because this study was retrospective, minor surgical complications may not have been reported. Participants did not undergo standardized evaluations for mesh-related complications, which may have resulted in under-reporting. Also, only complications requiring hospital admission were captured. Further, quality of life, sexual function, and patient satisfaction data were not readily available. The authors call for improved postmarketing studies and diligence on the part of physicians to properly counsel patients and monitor adverse events.

Serati M, Ghezzi F, Cattoni E, Braga A, Siesto G, Torella M, et al,. Tension-free vaginal tape for the treatment for urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. Eur Urology 2012;61:939-946.

This prospective study reports the long-term subjective, objective and urodynamic outcomes of women who have been followed for at least 10 years after retropubic TVT placement for SUI. Surgeries were performed at a single center in Varese, Italy, between January 2000 and June 2001. Patients were excluded if they had had prior incontinence or radical pelvic surgery, psychiatric or neurologic disorders, concomitant vaginal prolapse > PDO-Q Stage 1, urodynamically proven detrusor overactivity or postvoid residual > 100 mL. Preoperative evaluations included medical history, physical exam, a frequency/volume chart, urinalysis, and complete urodynamic testing. All surgeries were performed by the same surgeon. Follow-up evaluations included anamnestic and physical exam, cough test, and evaluation of subject satisfaction. Urodynamic testing was performed at the 10-year follow-up visit, or in the case of de novo overactive bladder symptoms. Urodynamic cure was defined as the absence of leakage during provocative maneuvers.

During the study period, 207 women were assessed for SUI; of these, 63 met eligibility criteria and underwent the TVT procedure. Bladder perforation occurred during surgery in two cases and in both cases the tape was promptly removed and replaced. No severe bleeding or other perioperative complications occurred. No postoperative complications requiring surgical intervention occurred. By the 10-year follow-up, 58 patients were available for evaluation. No significant deterioration in subjective or objective outcomes was observed over time. For example, percent of patients who rated themselves as satisfied plus improved was 95.2% at the 3-month follow-up and 93.1% at the 10-year follow-up. Objective cures by stress testing were 95.2% at three months and 93.1% at 10 years. The onset of de novo overactive bladder symptoms were reported by 30.1% of patients at the 3-month follow-up and 18.9% of patients at the 10-year follow-up. Two patients reported voiding difficulties at 10 years. No patient required tape release or section during the follow-up period. No significant vaginal prolapse, erosion or de novo dyspareunia were observed.

The authors conclude that TVT is a highly effective option for the treatment of SUI, with high cure rates and low complication rates. The early postoperative symptom of overactive bladder, particularly if persisting, could be the most relevant clinical issue related to TVT.

[Note: At the time this study was published, the authors considered TVT and TVT-O the gold standards for treatment of SUI.]

LITERATURE REVIEWS/META-ANALYSES

Bhargava S, Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.

This article is a review of current literature at the time (references cited dated from 1995 to 2004) on the complications of synthetic suburethral slings for the treatment of SUI.

Background

Until the introduction of the TVT procedure, the Burch colposuspension was considered the gold standard surgical procedure for the treatment of SUI. Sling procedures were first described in 1888 and have used autologous tissue, cadaveric tissue, and synthetic materials. Synthetic slings offer the advantage of reduction in morbidity of harvesting tissue from a second site, shortened operative time, early postoperative recovery, and an unlimited supply. The estimated number of TVT procedures from being introduced by Ulmsten and Petros until the present review was 600,000 cases worldwide. At publication, the transobturator (TVT-O) approach had been gaining interest. Recognized complications of sling procedures were de novo urgency, urge incontinence, incomplete bladder emptying and urinary retention, and urethral, bladder and vaginal erosion. Retropubic placement (Ulmsten procedure) is subject to complications such as bleeding, retropubic hematoma, and injury to adjacent structures. Complications may be due to the technique of sling placement or the material used. To minimize such complications, alternative techniques have been developed, such as TVT-O and a prepubic modification of TVT, although at the time this review was published, were not in general use.

Findings

The most frequent intraoperative complication of TVT placement is bladder perforation, with higher rates associated with patients who had undergone previous incontinence surgery. Injuries to other organs are rare and usually seen in difficult cases, such as in patients who have had multiple previous surgeries. Bleeding may also be a problem, but may not require any intervention. Intervention rates of 2.9% and 0.5% have been reported.

De novo urgency is reported in up to 20% of patients undergoing sling procedures, and 6-15% of patients undergoing TVT. It is thought that the symptoms are due to a combination of degree of obstruction and irritative symptoms due to the sling. Bladder neck elevation could also result in the development of voiding difficulty. Urinary retention may depend on operative factors such as sling placement and tension. A large multicenter randomized trial reported that 3% of patients required catheterization beyond the fourth postoperative week. This was usually managed by urethral dilatation. In other studies, urinary retention rates after TVT range from 2%-9%.

Sling erosion has been one of the most frequent and potentially serious complications with the use of synthetic slings. The introduction of newer sling materials such as loosely

woven polypropylene mesh (TVT, SPARC) appear to have reduced the incidence of erosion, and recent studies report incidences between 0.3% and 4.4%. In addition, the use of antibiotic prophylaxis and vaginal disinfection likely is a factor in the reduced erosion rates.

The authors conclude that, although complication rates are declining, possibly due to better surgical techniques, some can be devastating, and further work needs to be done on patient selection, development of safer techniques, development of a more ideal sling material, and conducting adequately powered randomized studies.

Atherton MJ, Stanton SL. The tension-free vaginal tape reviewed: an evidence-based review from inception to current status. BJOG 2005;112:534-546.

This article presents a review of Medline literature from 1990-2003. References were hand-searched, as were abstracts from the International Continence Society and International Urogynecological Association Annual Scientific Meetings from 1997-2003. All major comparative and non-comparative studies, as well as studies addressing specific issues on TVT were included.

The authors' review found that most early publications should be viewed as observational case studies without a comparison group risk bias. Similarly, although comparative data are available, most long-term studies are also observational and should be viewed with caution.

The authors conclude that the TVT has evolved over a short time scale into an acceptable surgical treatment for stress incontinence. It seems cost effective, with quicker recovery, and potentially carries less morbidity than conventional retropubic procedures, while providing good medium and long term success rates. The tape supports the mid-urethra, with the mechanism of continence thought to be dynamic urethral kinking. The tape may not significantly elevate the resting position of the bladder neck or urethra, and therefore potentially leads to less postoperative voiding difficulty, although emerging data suggest there is a trend towards an obstructive picture, which might be at the level of the mid-urethra. High success and low morbidity rates are promising. However, much of the data are from non-peer-reviewed small case series often "published" as abstracts. As a result, the conclusions should be interpreted cautiously. More information on the specific clinical issues presented in this review, the tissue reaction around the tape and the management of complications are awaited. Two-year comparative data and the five-to seven-year non-comparative data are promising. However, large, randomized studies with follow-up to five years are required to firmly establish the TVT as a safe, effective, longterm remedy for stress incontinence. In the meantime, the NICE has performed an appraisal of the TVT and has "recommended tension-free vaginal tape as one option for the surgical treatment of women with stress incontinence whenever non-surgical treatments (such as pelvic floor exercises) have not worked."

Deng DY, Rutman M, Raz S, Rodriguez LV. Presentation and management of major complications of midurethral slings: Are complications under-reported? Neurourology Urodynamics 2007;26:46-52.

In this retrospective article, the authors present their experience, as a tertiary referral center (UCLA), with major complications of mid-urethral slings. They also present a review of the literature and the results of a search of the FDA's MAUDE database.

From June 2001 and August 2005, 26 patients referred to UCLA for complications after placement of a sling were reviewed for history, sling type, presenting symptoms, time of onset of symptoms, type of complication, and treatment required. Types of slings included TVT (12 patients), SPARC (9), and transobturator (TO, 5). Details of the presentation and management of complications are shown in the table below.

Presentation and Management of Complications				
	Symptoms	**Time of Onset**	**Findings**	**Treatment**
TVT				
	Difficulty emptying	1 week	Mesh in urethra	Excision and reconstruction
	Retention, urethral pain	Immediate	Mesh in urethra	Excision and reconstruction
	Retention, urethral pain, UTI	Immediate	Mesh in urethra and bladder with calcification	Bladder excision, urethral excision and reconstruction
	Pelvic pain	Immediate	Mesh in bladder	Bladder excision
	Urgency, persistent SUI	Immediate	Mesh in urethra	Excision and reconstruction
	Urgency, urge incontinence, suprapubic pain	Immediate	Mesh in urethra and bladder	Bladder excision, urethral excision and reconstruction
	Severe mixed incontinence, suprapubic pain	2 weeks	Mesh in urethra	Excision and reconstruction
	Retention, urgency, urinary incontinence, urethral and vaginal pain	1 week	Mesh in urethra	Excision and reconstruction
	Urethral and perineal pain, tape released six months later, symptoms persisted	Immediate	Mesh in urethra	Excision and reconstruction
	Retention and pain, tape released seven months later, persistent urethral pain	1 week	Mesh in urethra with urethrovaginal fistula at 2 o'clock position	Excision and Martius flap

Presentation and Management of Complications				
	Symptoms	**Time of Onset**	**Findings**	**Treatment**
	Retention, tape incised four weeks later, persistent retention, urgency refractory to anticholinergics	Immediate	Mesh in proximal urethra and bladder	Bladder excision, excision of mesh from urethra, and reconstruction
	Urethral pain, then worsening incontinence	2 weeks	Mesh in urethra + urethrovaginal fistula	Excision and Martius flap
TO				
	Pain in labia and leg	1 week	Obturator abscess, vaginal erosion	Excision of mesh, drainage of obturator fossa
	Difficulty with adducting leg	Immediate	Nerve injury/entrapment	Excision of mesh
	Suprapubic pain, persistent incontinence	1 week	Mesh in bladder neck	Excision and reconstruction
	Frequency, urgency	1 week	Mesh in urethra	Excision and reconstruction
	Difficulty walking	2 weeks	Obturator abscess, vaginal erosion	Excision of mesh, drainage of obturator fossa
SPARC				
	Urgency, mixed incontinence	Immediate	Mesh at bladder neck	Excision and reconstruction
	Retention, abdominal pain	Immediate	Mesh in urethra	Excision and reconstruction
	Retention, sling released after four weeks	2 weeks	Mesh in urethra	Excision and reconstruction
	Urgency, incontinence	3 weeks	Mesh in bladder	Bladder excision
	Persistent incontinence	6 weeks	Urethrovaginal fistula	Urethrovaginal fistula repair with Martius flap
	Urgency, urge incontinence, poor emptying bladder stones, endoscopic management of stones	2 weeks	Mesh in urethra and bladder with calcification	Bladder excision, excision of mesh from urethra, and reconstruction
	Frequency, worsening incontinence	1 week	Mesh traversing bladder neck to bladder	Partial cystectomy

Presentation and Management of Complications				
	Symptoms	**Time of Onset**	**Findings**	**Treatment**
	Retention in recovery, unable to pass urethral catheter, back to operating room, suprapubic tube placed, and sling cut	Immediate	Mesh in urethra, necrotic proximal urethra	Excision and Martius flap
	Frequency, persistent SUI	2 weeks	Mesh in urethra + urethral diverticulum	Excision and reconstruction

A review of the literature revealed 28 studies on mid-urethral slings that included complications in the analysis. Of these, 14 studies used mid-urethral slings (TVT or SPARC) and 14 used TO slings. Only 86 major complications out of 11,806 patients were reported (0.7%). Complications included bowel perforation (three patients), vascular injury (two patients), nerve injury (six patients), unrecognized bladder perforation (14 patients), unrecognized urethral injury (seven patients), transfusion or significant bleeding (19 patients), hematoma requiring surgical reoperation (29 patients), and abscess requiring surgical drainage (six patients).

The FDA MAUDE database included 928 reported complications, of which 161 were considered major. Types of slings involved were TVT (700), SPARC (66), TVT-O (1, Gynecare, Ethicon), ObTape (149), and Monarc (12). There were 154 major complications using retropubic slings, with eight reported deaths, and 162 major complications using TO slings, with two reported deaths.

The authors note the discrepancy in reporting of major complications between the literature and the MAUDE database. They point out that, in the absence of a national registry for all sling procedures, the true denominator is unknown, and therefore an incidence for major or minor complications cannot be calculated, nor can quantitative comparisons be made between the published literature and the MAUDE database. However, the fact that 10 deaths after sling procedures were reported to MAUDE, and none appear in the literature of over 11,000 patients is difficult to explain. The discrepancy may be due to differences in surgeon training and experience, lack of long-term follow-up for some patients, failure to recognize a possible cause and effect of post-surgical complications, and a tendency for voluntary reporting to MAUDE to skew to the more serious complications. The authors state that practitioners of SUI surgery tend to rely on the published literature as representative data, and therefore may not be aware that sling procedures may be associated with a significant risk of morbidity and mortality. They conclude that prospective randomized studies and reporting of complications by all practitioners is necessary to minimize future complications and failures.

Latthe PM, Foon R, Toozs-Hobson P. Transobturator and retropubic tape procedures in stress urinary incontinence: a systematic review and meta-analysis of effectiveness and complications. BJOG 2007;114:522-531.

TVT: tension-free vaginal tape
TOT: outside-in transobturator
TVT-O: inside-out transobturator

In this literature review, MEDLINE, EMBASE, CINAHL, LILIACS (up to September 2006), CENTRAL (The Cochrane Library, Issue 3, 2006), MetaRegister of Controlled Trials, The National Library for Health, the National Research Register, and Google Scholar were searched using various relevant search terms. Randomized controlled trials (RCTs) that compared the effectiveness of TVT-O or TOT with synthetic tension-free vaginal tape (TVT) by retropubic route (Gynecare; Ethicon Inc., NJ, USA) for the treatment of SUI in all languages were included. Two reviewers extracted data on participants' characteristics, study quality, population, intervention, cure, and adverse effects independently.

Five RCTs compared TVT-O with TVT, and six RCTs compared TOT with TVT. When compared by subjective cure, TVT-O and TOT at two to 12 months were no better than TVT (OR 0.85; 95% CI 0.60–1.21). Adverse events such as bladder injuries (OR 0.12; 95% CI 0.05–0.33) and voiding difficulties (OR 0.55; 95% CI 0.31–0.98) were less common, whereas groin/thigh pain (OR 8.28; 95% CI 2.7–25.4), vaginal injuries or erosion of mesh (OR 1.96; 95% CI 0.87–4.39) were more common after tape insertion by the transobturator route.

The authors concluded that the evidence for short-term superiority of effectiveness of TOT is currently limited. Bladder injuries and voiding difficulties are lower, but the risk of vaginal erosions and groin pain is higher with TVT-O/TOT. Methodologically sound and sufficiently powered RCTs with long-term follow-up are needed.

Twiss C, Raz S. Complications of synthetic mid-urethral slings. Issues in Incontinence, Laborie.com, Spring/Summer 2008.

[Note that Laborie is a manufacturer of devices for urology and gynecology.]

The purpose of this literature review is to summarize the rates, etiology, and management of the most common complications encountered with synthetic mid-urethral slings, and to compare complication rates of the retropubic and transobturator approaches.

Bleeding

One of the difficulties in assessing bleeding complications of synthetic sling placement is that "bleeding" as a complication has no firm definition or criteria. There is great variability in the literature in reporting and assessing the degree of bleeding. When placing retropubic slings, a common source of troublesome bleeding is inadvertent

deviation of the trocar within the retropubic space, either too close to the urethra, leading to bleeding from the periurethral venous complex, or too lateral, leading to venous bleeding from vessels on the pelvic sidewall. Careful control of trocar placement reduces the potential for bleeding from these sites.

One of the largest series to report bleeding after retropubic placement of synthetic slings is an Austrian registry of 5,578 tension-free vaginal tape (TVT) procedures, which showed an overall 2.7% rate of bleeding complications with 0.8% requiring reoperation, primarily via laparotomy. Other large TVT series report rates of hemorrhage/hematoma between 1.9% and 2.7%. However, when routine pelvic magnetic resonance imaging (MRI) was performed after retropubic sling procedures, 25% of patients were found to have clinically unsuspected retropubic hematomas. The authors conclude that while significant bleeding is possible after retropubic sling placement, major, clinically overt bleeding is uncommon.

More recent evidence suggests that bleeding is significantly reduced with the transobturator approach to mid-urethral sling placement. Several large series fail to report any significant bleeding complications with the technique. The meta-analysis of randomized controlled trials by Sung et al., comparing retropubic with transobturator slings, found that the rate of significant hematoma was 1.6% for the retropubic approach, compared to 0.08% for the transobturator approach. Similarly, in the recent meta-analysis by Novara et al., the odds ratio of pelvic hematoma was 4.83 for retropubic as compared to transobturator slings. However, despite this evidence, significant bleeding, including iliac and obturator vessel injury, has been reported with use of the transobturator technique. Thus, although there is a consensus that transobturator sling procedures carry significantly less bleeding risk compared to retropubic mid-urethral sling procedures, transobturator sling placements are by no means immune to bleeding complications, and careful attention must be paid to proper technique.

Perforations and Erosions

Bladder perforation is one of the more common intraoperative problems encountered with retropubic mid-urethral sling placement, occurring in 2.7%–6% in large series. Bladder perforation during retropubic sling placement occurs more commonly in patients with a history of anti-incontinence procedures, likely due to scarring within the retropubic space. Bladder perforation occurs less frequently with the transobturator approach compared to the retropubic approach, with reported rates of bladder perforation between 0% and 1.5% with this technique. Urethral perforation remains rare for both retropubic and transobturator approaches, but it can occur with either. Intraoperative urethral injury has been reported in 0.07%–0.2% of retropubic sling cases, and 0.1%–2.5% of transobturator sling cases. This complication typically requires a formal repair of the damaged area, and is somewhat more serious than bladder perforation.

Bowel perforation is a potentially lethal complication that typically occurs when the retropubic approach is utilized in patients with bowel adhesions in the retropubic space due to prior abdominal surgeries. Bowel perforation is rare, reported to occur in 0.03%–

0.7% of retropubic sling cases. The risk of this complication is greatly reduced with use of the transobturator approach because it specifically avoids entry into the retropubic space.

Postoperative vaginal erosions are another problem with synthetic slings. Meta-analyses of randomized trials comparing retropubic with transobturator synthetic slings fail to demonstrate a significant difference in vaginal erosion rates between the two techniques. Large case series of TVT and SPARC-sling procedures report that vaginal erosions are rare, occurring in 0.2%–1.8% of cases.

The most important factor in preventing vaginal erosions appears to be choice of synthetic sling material. Soft, woven, monofilament polypropylene mesh with large (> 75 microns) pore size appears to be the mesh of choice, as it allows proper incorporation of the mesh into host tissue and facilitates immune surveillance. There is currently no evidence-based consensus on the management of vaginal erosions.

Groin and Thigh Complications

Groin and thigh complications are significantly more prevalent with transobturator slings than retropubic slings, and can be life threatening in some cases. A meta-analysis of 17 randomized controlled trials comparing retropubic with transobturator slings, found that the odds ratio of groin/thigh pain was 8.3 for transobturator, as compared to retropubic slings, and the large French registry of TVT-O procedures reported a 2.7% rate of residual pain lasting greater than four weeks duration. More significant is that serious infectious complications resulting from transobturator slings have been reported, including groin and thigh abscesses, sepsis, and gangrene. While transobturator sling procedures are often marketed as “less invasive” due to avoidance of the retropubic space, transobturator slings are placed into an anatomic region that is very difficult to access after the sling is placed. Removal of retropubic slings remains relatively straightforward, especially because urologists and gynecologists are familiar with the anatomy of the retropubic space and urethra. Conversely, removal of a transobturator sling remains challenging because it occupies a deep tissue space that is difficult to access, and the anatomy of this region is far less familiar to pelvic surgeons. Thus, both retropubic and transobturator sling procedures are “invasive,” and each sling carries its own set of problems associated with the anatomic region that it occupies.

Postoperative Voiding Dysfunction

Recent evidence suggests that de-novo urgency after sling placement is relatively common, occurring in 10%–15% of cases; however, the range in the literature spans a 10-fold difference, from 3.1% to 32%. Recent meta-analyses of randomized trials comparing retropubic to transobturator slings are conflicting.

Postoperative urinary obstruction can be a serious complication after sling surgery, and the incidence remains difficult to assess, primarily due to the fact that the diagnosis is not always straightforward. A recent review of the Medicare data on 1,356 sling procedures

found that within the first postoperative year there was a new diagnosis of obstruction in 7% of cases, and treatment for obstruction in 8% of cases. The AUA Female Stress Urinary Incontinence Clinical Guidelines Panel estimated the overall risk of permanent, and temporary (< five weeks) postoperative urinary retention after sling surgery to be 5% and 8%, respectively. A recent study by Morey et al. and two recent meta-analyses suggest that obstructive complications are more common after retropubic as compared to transobturator sling procedures; this may reflect the difference in shape of the two types of slings, but this concept is currently unproven.

Under-Reporting of Complications

Despite that many series report complications with synthetic mid-urethral slings, there is compelling evidence that these complications remain under-reported in the literature. Deng et al. recently reviewed the MAUDE (Manufacturer and User Facility Device Experience) database and identified 161 major complications that included 39 vascular injuries, 38 bowel injuries, and 10 deaths due to surgical complications of synthetic sling placement. In the same study, the ratio of major to total complications in the MAUDE database as compared to literature review suggested significant under-reporting of major complications resulting from synthetic sling placement. Another recent review of the MAUDE database found similar underreporting of complications of transobturator sling placement.

Conclusions

Collective experience has revealed overall good safety and efficacy when proper attention is paid to technique, and selection of sling material. However, clinicians must remain aware that significant and even lethal complications are possible despite the minimally invasive nature of synthetic mid-urethral sling placement, and that complications of these procedures remain underreported in the literature. While the transobturator approach causes fewer bleeding and visceral perforation complications due to avoidance of the retropubic space, it carries its own set of complications associated with placement into the obturator space, which can pose challenging management problems.

Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane Review. Neurol Urodynam 2011;30:284-291.

This is an abridged version of the 2010 Cochrane review of the effects of minimally invasive clings for the treatment of SUI. Both retropubic and transobturator surgeries are included in this review. Searches of the Cochrane Incontinence Group Specialised Register (searched March 20, 2008), MEDLINE (January 1950--April 2008), EMBASE (January 1988--April 2008), CINAHL (January 1982--April 2008), AMED (January 1985--April 2008), the UK National Research Register, ClinicalTrials.gov, and reference lists of relevant articles were conducted. Randomized or quasi-randomized controlled trials amongst women with SUI, urodynamic stress incontinence (USI), or symptoms of

stress or mixed urinary incontinence (MUI), in which at least one trial arm involved a minimally invasive synthetic suburethral sling operation, were included. Two review authors assessed the methodological quality of potentially eligible studies and independently extracted data from the included trials.

Sixty-two trials involving 7,101 women were included. The quality of evidence was moderate for most trials. Minimally invasive synthetic suburethral sling operations appeared to be as effective as traditional suburethral slings [eight trials, n=599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94--1.13], but with shorter operating time and less postoperative voiding dysfunction and de novo urgency symptoms. Minimally invasive synthetic suburethral sling operations appeared to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90--1.03; at five years RR 0.91, 95% CI: 0.74--1.12) with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time and hospital stay, but significantly more bladder perforations (6% versus 1%, RR 4.24, 95% CI: 1.71--10.52). There was conflicting evidence about the effectiveness of minimally invasive synthetic suburethral sling operations compared to laparoscopic colposuspension in the short term (objective cure, RR 1.15, 95% CI: 1.06--1.24; subjective cure RR 1.11, 95% CI: 0.99--1.24). Minimally invasive synthetic suburethral sling operations had significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities. A retropubic bottom-to-top route was more effective than top-to-bottom route (RR 1.10, 95% CI: 1.01--1.20; RR 1.06, 95% CI: 1.01--1.11), and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions. Monofilament tapes had significantly higher objective cure rates (RR 1.15, 95% CI: 1.02--1.30) compared to multifilament tapes and fewer tape erosions (1.3% versus 6% RR 0.25, 95% CI: 0.06--1.00). The obturator route was less favorable than the retropubic route in objective cure (84% versus 88%; RR 0.96, 95% CI: 0.93--0.99; 17 trials, n=2,434), although there was no difference in subjective cure rates. However, there was less voiding dysfunction, blood loss, bladder perforation (0.3% versus 5.5%, RR 0.14, 95% CI: 0.07--0.26), and shorter operating time with the obturator route.

The authors concluded that current evidence base suggests that minimally invasive synthetic suburethral sling operations are as effective as traditional suburethral slings, open retropubic colposuspension and laparoscopic colposuspension in the short-term but with less postoperative complications. Objective cure rates are higher with retropubic tapes than with obturator tapes, but retropubic tapes attract more complications. Most of the trials had short-term follow-up, and the quality of the evidence was variable.

CASE STUDIES

Sweat SD, Itano NB, Clemens JQ, Bushman W, Gruenenfelder J, McGuire EJ, et al. Polypropylene mesh tape for stress urinary incontinence: complications of urethral erosion and outlet obstruction. J Urol 2002;168:1440146.

In this article, the records of five patients with difficulty voiding and/or gross hematuria after placement of polypropylene mesh tape (Gynecare, Ethicon) were reviewed. Patients presented between two and 14 months after surgery, and were evaluated by history, physical exam, urine testing, and cystoscopy. Graft erosion was documented in three patients. Two patients had urethral erosion, and another had vaginal and bladder wall erosion. The slings were explanted in all three patients. The authors felt that the apparent cause of the erosions was inappropriate placement of the tape through the tissue planes, or placement under tension. Also, one patient was not an appropriate candidate for the TVT procedure, because she had comorbidities of neurogenic bladder, bowel dysfunction, and a denervated sphincter. The authors state that theirs is the first report of urethral erosion, permanent retention necessitating urethrolysis, or mesh infection in the purportedly more than 100,000 TVT procedures performed worldwide up to this point in time.

Kwon SY, Latchamsetty KC, Benson J, Carreno M. Inflammatory myofibroblastic tumor of the urinary tract following a TVT. Female Pelvic Med Reconstruct Surg 2012;18:249-251.

This is a case report of a patient who presented with gross hematuria, urinary urgency and frequency, and dysuria 10 weeks after placement of TVT (Gynecare) for urodynamically confirmed SUI. A large solid mass was palpable retropubically on pelvic exam and confirmed by CT and MRI. When compared with a CT scan done before TVT placement, it was confirmed that the mass developed after TVT placement. She was eventually diagnosed with an inflammatory myofibroblastic tumor (IMT) and underwent a trans-urethral resection with complete resolution of symptoms and no recurrence two years later.

Although rare, postoperative IMTs have been known to follow manipulation of the bladder by biopsy, injury or resection. This is the first report of such an occurrence after TVT placement. The authors state that the patient did not have a visible bladder injury at the time of mesh placement; it is possible that the muscularis layer may have been inadvertently breached without actual perforation. This patient also had a history of neurofibromatosis, but the authors state that no information in the literature suggested a relationship between that condition and the IMT.